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1. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Méd., vol. 3 (July) 1950.

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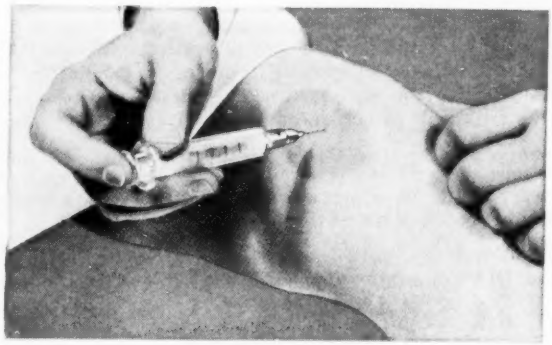

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1. Brown, E. M., Frain, J. B., Udell, L., and Hollander, J. L.: Paper presented at Annual Meeting, American Rheumatism Association, Chicago, Ill., June 6, 1952.

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1. Bargen: Chronic Ulcerative Colitis. Charles C Thomas, Publisher, 1951—Springfield, Illinois.
2. Morrison, Lester M.: Results of treatment of ulcerative colitis with salicylazosulfapyridine. Gastroenterology, 21, 133 (1952).

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1. Greenhill, J. P.: Principles and Practice of Obstetrics, ed. 10, Philadelphia, W. B. Saunders Company, 1951, pp. 103-104; 311; 332.

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 92 JULY 1953 NUMBER 1

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Editorials

MANAGEMENT OF THE CARDIAC PATIENT IN A HOT AND HUMID ENVIRONMENT

IT HAS been noted that a hot and humid environment precipitated acute congestive heart failure in patients who are compensated sufficiently to be comfortable when at rest in bed in a comfortable environment.[1] Failure was precipitated more readily if the patients were removed from a comfortable room atmosphere to a given hot and humid environment in the laboratory during the winter season than during the summer. This difference may be an expression of physiologic adjustments of acclimatization. That acclimatization is responsible for this apparent seasonal difference is supported by the well-known high fatality rates during sudden severe heat waves which occur in the cooler areas of this country and the relatively low rates in the warmer areas.[2]

The fact that a hot and humid environment precipitates acute congestive heart failure is not surprising when it is realized that such environmental conditions produce an extra load or stress upon the cardiovascular system, evidenced in part by an increase in cardiac output and cardiac work.[3] Such an environment is a strong stimulus to the central and peripheral portions of the vascular system and results in changes designed to maintain thermal equilibrium. The cardiovascular system will attempt to eliminate body heat to the environment, but if it is sufficiently hot and humid only a slow rate of loss of body heat may be possible or, in fact, the body may even gain heat from the environment. When the latter situation exists, the cardiovascular adjustments designed to increase the rate of heat loss actually operate to increase the rate of heat gain by the body. Normally, when a man enters a hot and humid environment, the primary cardiovascular changes which take place are

1. Burch, G. E.: Influence of Environmental Temperature and Relative Humidity on the Rate of Water Loss Through the Skin in Congestive Heart Failure in a Subtropical Climate, Am. J. M. Sc. **211**:181-188 (Feb.) 1946. Berenson, G., and Burch, G. E.: The Response of Patients with Congestive Heart Failure to Rapid Elevation in Atmospheric Temperature and Humidity, ibid. **223**:45-53 (Jan.) 1952.

2. Ferris, E. B., Jr.; Blankenhorn, M. A.; Robinson, H. W., and Cullen, G. E.: Heat Stroke: Clinical and Chemical Observations on 44 Cases, J. Clin. Invest. **17**:249-262 (May) 1938.

3. (*a*) Burch, G. E.: The Normal and Abnormal Physiologic Effects of Tropical Climate, New Orleans M. & S. J. **98**:14-31 (July) 1945. (*b*) Asmussen, E.: Cardiac Output in Rest and Work in Humid Heat, Am. J. Physiol. **131**:54-59 (Nov.) 1940. (*c*) Taylor, H. L.; Henschel, A. F., and Keys, A.: Cardiovascular Adjustments of Man in Rest and Work During Exposure to Dry Heat, ibid. **139**:583-591 (Aug.) 1943. (*d*) Bazett, H. C.: Physiological Responses to Heat, Physiol. Rev. **7**:531-599 (Oct.) 1927; (*e*) The Effect of Heat on the Blood Volume and Circulation, J. A. M. A. **111**:1841-1845 (Nov. 12) 1938. (*f*) Byfield, G. V.; Telser, S. E., and Keeton, R. W.: Renal Blood Flow and Glomerular Filtration as Influenced by Environmental Temperature Changes, ibid. **121**:118-123 (Jan. 9) 1943.

acceleration in pulse rate, vasodilatation of the vessels of the skin, vasocontriction of the vessels of the viscera and nondermal organs, increase in linear rate of blood flow (circulation time), increase in cardiac output, and rise in pulse pressure, usually due to an elevation in systolic blood pressare and at times to a fall in diastolic blood pressure. The changes appear to be primarily directed toward assuring a high rate of blood flow through the skin, from which heat may be removed from the body by conduction, convection, radiation, and evaporation of sweat. When the environment is hot and humid, heat loss by all four processes is impaired, or there may even be a gain of heat if the temperature and humidity are sufficiently high. A hot and humid environment can produce physiologic changes which may even result in death of the individual.

A hot and humid environment has essentially the same influence as physical exertion upon cardiac work and cardiac reserve. The cardiac output may be increased 100% in normal man.[3e] In fact, the influence of a hot and humid environment upon cardiac output and work has been studied little in man, so that it is not known precisely what levels cardiac output may attain at various thermal and humidity levels for normal man at rest and with exertion. Such studies have certainly been neglected for man with cardiac disease. The cardiac stress produced apparently varies directly with the stimulus, which depends upon the height of the temperature and relative humidity as well as the amount of physical exertion. From the cardiac point of view, placing a patient in a warm or hot and humid environment may be equivalent to having him run around the hospital.

It is evident that the cardiac patient should be placed in an environment which is comfortable to him and which permits maintenance of thermal equilibrium without any stress upon the cardiovascular system. The most desirable level of temperature and humidity for the cardiac patient is not well known. In fact, the textbooks and monographs of medicine and cardiology as well as the medical literature as a whole neglect this important factor in therapy. In view of wide individual variations, differences in bed clothing, activity on the part of the patient and climate from one area of a country to the next, as well as seasonal variations, the best guide in adjusting the room temperature and humidity is the patient's comfort. This is usually satisfactory if the patient is mentally alert. When he is not, then 75 F. (about 24 C.) and not more than 60% relative humidity are suitable atmospheric conditions. The oxygen tent should be used on hot and humid days primarily for the thermal influences rather than for the oxygen itself. The importance of the thermal influences can be easily demonstrated by observing the cardiac patient's reaction first to closing off the oxygen supply to the tent and later to maintaining the oxygen supply and turning off the flow of the cooled air.

To place the cardiac patient in a warm bed in a hot and humid room for rest of the cardiovascular system may be, and usually is, therapeutically erroneous. The skeletal muscles may be at rest, but the heart and circulation will not be. It seems plausible that paroxysmal nocturnal dyspnea may be precipitated in part by the stress of a warm bed and bedroom, since the cardiovascular system is relieved when the patient walks to an open window or porch where cool air permits heat loss to occur without stress upon the heart and circulation. There is need for greater use of air-

conditioning of the cardiac patient's room, ward, or hospital. Bed rest in an air-conditioned room can assure cardiac rest, whereas bed rest in a warm bed and room may effect skeletal muscle rest but greater cardiac work. Furthermore, the subtle increase in cardiac work and stress brought about by a slightly warm environment may nullify the benefits of physical rest or even cause a gradual and constant stress upon the heart and circulation. Greater use of air-conditioning of the patient's room at home or in the hospital is essential if the patient's heart is to rest on hot and humid days, especially if this type of weather develops suddenly.

The stress of a hot and humid environment is, of course, intensified during physical exertion. This should be remembered when cardiac patients are given instructions. They should remain particularly inactive when the environment is hot and humid. Sudden and vigorous muscular exertion on a hot and humid day may be equivalent to our experiments in which acute cardiac asthma was precipitated by moving the patient with impairment of cardiac reserve from a comfortable environment to a hot and humid one. Strenuous exercise of performing chores around the home or garden induces more stress upon the cardiovascular system on hot and humid days than on cool ones. With acclimatization, however, man can perform more work with less physiologic disturbance than he can when not acclimatized, but even normal subjects, with acclimatization, cannot establish a satisfactory steady physiologic state in a hot and humid environment.

Another aspect of the influences of a hot and humid environment upon the circulation deserving comment is that related to the shifting of blood to the skin at the expense of the circulation to the other organs.[4] The blood flow to the skin may increase fifty-fold over the normal resting level.[5] There are essentially 5 liters of blood in the vessels of an average man. Normally and at rest about one-fifth circulates through the kidney, one-fifth through the brain, one-fifth through the liver, and the remainder through the other organs and tissues. The brain and heart receive preference in the distribution of blood. Because of the location of the coronary orifices at the root of the aorta, the heart is assured a blood supply if the blood pressure is maintained. Under the influence of the strong stimulus of a hot and humid environment, however, blood is shifted to the skin at the expense of the liver and kidneys and probably the brain. This shift apparently occurs even if it results in death of the organism. It is possible that the hemorrhages in the brain resulting from a hot and humid environment are due to cerebral anoxia associated with the shifting of blood away from the brain. Renal function declines precipitously and the circulation to other organs may become seriously impaired. As noted from plethysmographic studies, there is lending and borrowing of blood among various tissues and organs from the 5-liter pool of blood, previously termed hemometakinesia.[4a] A hot and humid environment results in obligatory "lending" of blood to the dermal circulation even if serious impairment of the function of the more vital organs, such as brain, heart, kidneys, and liver, ensues. With impaired cardiac reserve, any compensating

4. (*a*) Ray, T.; Burch, G. E., and DeBakey, M. E.: The "Borrowing-Lending" Hemodynamic Phenomenon (Hemometakinesia) and Its Therapeutic Application in Peripheral Vascular Disturbances, New Orleans M. & S. J. **100**:6-15 (July) 1947. (*b*) Footnote 3 *d*, *e*.

5. Sundstroem, E. S.: The Physiological Effects of Tropical Climate, Physiol. Rev. **7**:320-362 (April) 1927.

increase in cardiac output will be limited or impossible, with the result that borrowing of blood occurs with detriment to the vital structures.

Thus, it becomes evident that with disease of any of the vital organs besides the heart, a comfortable and cool environment should be maintained to prevent unnecessary shifting of blood away from any of these diseased organs where blood is so necessary to the skin for thermal regulation.[6] To prevent cardiac stress or local impairment of the circulation in organs, the patient who has disease of the heart, local viscera, or organs and who needs adequate circulation to the vital internal visceral structures should remain in a comfortable environment even if air-conditioning equipment is required. This is an aspect of therapy too often neglected in cardiac disease and visceral disease.

G. E. BURCH, M.D.

6. Field, J., II, and Hall, V. E.: Physiological Effects of Heat and Cold, Ann. Rev. Physiol. **6**:69-94, 1944.

THE THYROID GLAND IN RELATION TO NEUROMUSCULAR DISEASE

CLARK H. MILLIKAN, M.D.
AND
SAMUEL F. HAINES, M.D.
ROCHESTER, MINN.

IN 1895 Bathurst [1] described a patient who had exophthalmic goiter and severe muscle wasting. Apparently this is the first instance in which sharp attention was focused on the possible existence of a relationship between muscle function and the thyroid gland. The literature concerning this subject is not voluminous, even now. In 1938, Starling, Darke, Hunt, and Brain [2] suggested the following classification for a number of disorders in which thyroid and muscle dysfunction were associated:

1. Exophthalmic ophthalmoplegia
2. Thyrotoxic myopathy
   A. Acute thyrotoxic myopathy
   B. Chronic thyrotoxic myopathy
   C. Thyrotoxic periodic paralysis
3. Myasthenia gravis and thyrotoxicosis

The cases cited as evidence for the existence of "acute thyrotoxic myopathy" are few and inconclusive. The patient reported by Heuer [3] in 1916 probably had thyrotoxicosis associated with myasthenia gravis. Sheldon and Walker [4] wrote concerning acute thyrotoxic myopathy in 1946. The one patient on whom data were reported was extremely weak but was made "almost normal" by the administration of neostigmine. We have not seen such an entity and believe that this would appear to be hyperthyroidism associated with myasthenia gravis. We have not seen neostigmine give relief from the weakness of hyperthyroidism. Until more adequate evidence accumulates to document the existence of the foregoing disorder

---

Read at the meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 12 and 13, 1952.

From the Sections of Neurology and Psychiatry (Dr. Millikan) and the Division of Medicine (Dr. Haines), Mayo Clinic.

1. Bathurst, L. W.: A Case of Graves' Disease Associated with Idiopathic Muscular Atrophy: Remarks, Lancet **2**:529-530 (Aug. 31) 1895.

2. Starling, H. J.; Darke, C. S.; Hunt, B. W., and Brain, W. R.: Two Cases of Graves's Disease With Muscular Atrophy, Guy's Hosp. Rep. **88**:117-128 (Jan.) 1938.

3. Heuer, G. J.: The Cerebral Nerve Disturbances in Exophthalmic Goiter, Am. J. M. Sc. **151**:339-351 (March) 1916.

4. Sheldon, J. H., and Walker, R. M.: Acute Thyrotoxic Myopathy: Recovery After Partial Thyroidectomy, Lancet **1**:342-343 (March 9) 1946.

and because new observations concerning thyroid and muscle have appeared in the literature, the following classification will be used in this discussion:

1. Thyrotoxicosis and
   A. Myasthenia gravis
   B. Chronic thyrotoxic myopathy
   C. Periodic paralysis
   D. Exophthalmic ophthalmoplegia
2. Hypothyroidism and altered muscle function

HYPERTHYROIDISM AND MYASTHENIA GRAVIS

In 1908 Rennie [5] reported details concerning a man, aged 27 years, who suffered from exophthalmos, external ophthalmoplegia, rapid exhaustion of the jaw muscles, weak trunk muscles, and easy exhaustion of the deep reflexes. Rennie believed that two diseases existed simultaneously in the patient. These were exophthalmic goiter and myasthenia gravis.

Since that time additional reports have accumulated in the literature concerning the relationship of the two disorders. Cohen and King [6] commented that similarities exist between the two diseases, that is, hypertrophy of lymphatic tissue, occasional lymphocytosis, glycosuria in certain instances, and the presence of lymphorrhages in muscle tissue. In 1939 Thorner [7] related details of the case of a woman, aged 20 years, in which the myasthenia gravis improved as the hyperthyroidism got worse and as the hyperthyroidism was treated the symptoms of myasthenia became more severe. The author wrote that this "represents a physiologic antagonism between hyperthyroidism and myasthenia gravis." Subsequently, thyroid was administered to patients who had myasthenia gravis but the degree of improvement did not justify the treatment.

Kowallis, Haines, and Pemberton [8] reported four cases in which the two disorders occurred simultaneously. Their second case was very similar to some alleged instances of "thyrotoxic myopathy" described elsewhere in the literature. In 1948 McEachern and Parnell [9] commented concerning the "see-saw relationship" between the two diseases, as demonstrated by their observations on two patients. In contrast, no such relationship was noted by Bartels and Kingsley [10] in four patients, each having both hyperthyroidism and myasthenia gravis. Levy, Meadows, and Gunnar [11] suggested, after treating five patients who had the two diseases, that

5. Rennie, G. E.: Exophthalmic Goitre Combined With Myasthenia Gravis, Rev. Neural. & Psychiat. **6**:229-233, 1908.

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severe hyperthyroidism should be treated when the two diseases coexist. This suggestion seems logical.

The detection of patients having two diseases such as myasthenia gravis and hyperthyroidism makes necessary the possession of knowledge concerning the diagnostic intricacies of each disease. Many internists are familiar with the clinical picture of hyperthyroidism, and this knowledge is supplemented by use of determinations of the basal metabolic rate, serum cholesterol, protein-bound iodine of the serum, uptake and urinary excretion of radioactive iodine, and, in some instances, the creatinine tolerance test. Because of its lower prevalence the diagnosis of myasthenia gravis is less well understood. A strengthening of objectively weak muscles following the hypodermic administration of neostigmine methylsulfate is often recorded as the sole criterion for the diagnosis of myasthenia gravis. However, not only are there instances of far-advanced myasthenia gravis in which response to this drug is mild or nonexistent but there are also instances in which the disease is relatively mild (partial or complete ophthalmoplegia) and the response to neostigmine is likewise mild or nonexistent. In the latter instance the diagnosis of myasthenia gravis may be missed entirely unless weakness subsequently develops which does respond to neostigmine or unless some additional test is used. The following case history illustrates this point.

A white man, 35 years of age, was first seen at the Mayo Clinic in July, 1952, at which time he complained of double vision and bilateral partial ptosis. (The double vision was due to incomplete ophthalmoplegia.) The patient stated that the double vision began in April, 1952. The local neurologist administered a test dose of neostigmine, but the ocular rotations did not improve. The patient was told that he had multiple sclerosis. Early in June partial ptosis was noted but the neostigmine test was not repeated. When the neostigmine test was done in July, 1952, there was moderate improvement in the ptosis and no change in the ophthalmoplegia. A curare test was performed. Almost complete ptosis, neck weakness, and shoulder girdle weakness developed when 1/180 of a curarizing dose was administered intravenously.

Some form of test using curare and neostigmine or the electromyogram often aids greatly in the diagnosis of certain cases of myasthenia gravis.

The 25 cases [12] of hyperthyroidism and myasthenia gravis to be presented here were examined and followed by one or more members of the sections of metabolism and the sections of neurology. In certain instances the diagnosis of one or both diseases was relatively simple, while in others a number of special tests were needed to establish the diagnosis.

REPORT OF CASES OF ASSOCIATED HYPERTHYROIDISM AND MYASTHENIA GRAVIS

CASE 1.—A woman, aged 43 years, underwent thyroidectomy in 1930 for definite hyperthyroidism and was well until two and one-half years before admission, which was in May, 1944. At that time she began to have weakness of the face, drooping of the eyelids, and weakness of the muscles all over the body, so that she was unable to get out of bed.

On physical examination there was found ptosis 2+/2+, ocular rotations —2 in all directions, and strength —2 in the shoulders and arms and —2 to —3 in the hands, while in the lower extremities the strength was normal to —1 except for the psoas muscles, which were —2. The hands and feet were warm and moist. The pulse rate was 138 per minute, blood pressure 160/60, and there was an enlarged nodular thyroid gland. The basal metabolic rate was +43%. There was no evidence of a tumor of the thymus. Since there was a definitely positive response to

12. Cases 9, 15, and 21 were originally reported by Kowallis, Haines, and Pemberton.[8]

neostigmine, a diagnosis of myasthenia gravis in addition to hyperthyroidism was made. Treatment was undertaken with thiouracil and neostigmine, but, while there was moderate improvement from the latter, the hyperthyroidism did not seem to respond particularly well. Word was ultimately received that the patient had died suddenly in bed in July, 1944.

CASE 2.—A woman, aged 63 years, registered at the clinic in April, 1944, at which time she complained of headache, some shortness of breath on exertion, and generalized weakness. The thyroid gland was not enlarged, the blood pressure was 150/80, and the pulse rate was 80. The basal metabolic rates were +26 and +25%, and roentgenograms of the chest revealed an anterior mediastinal tumor. A clinical diagnosis of hyperthyroidism was made. While the patient was visiting the clinic, some ptosis of the right eyelid developed, and when she was tested with curare a complete ptosis developed on the right within two minutes after the administration of 1/180 of a curarizing dose. There was marked improvement of this physical sign following the administration of neostigmine. The patient was treated with strong iodine solution, U.S.P. (Lugol's solution) and neostigmine. She returned to Rochester in September, 1944, at which time she was getting along fairly well. A follow-up letter revealed that she had died Dec. 5, 1945, apparently of respiratory insufficiency.

CASE 3.—A girl, aged 19 years, registered in May, 1942, at which time she complained that one year previously she had noted drooping of the left eyelid and double vision. A diagnosis of myasthenia gravis had been made at that time. When she was first examined at the clinic there was fairly marked ptosis of both eyelids, the left being more severely affected than the right. There were weakness of the right external rectus muscle and diplopia on looking to the left and up and down in the left lateral position. The ocular levators were all —4, and the left external rectus strength was —3. The blood pressure was 120/82, and the pulse rate was 110 per minute. The basal metabolic rate was +26%. Roentgenograms of the chest showed no abnormalities. A diagnosis of hyperthyroidism was made, and after neostigmine therapy, with improvement of the weakened muscles, a diagnosis of myasthenia gravis was also made. Thyroidectomy was performed. Follow-up of this patient revealed that she was seen in New York in 1945, at which time a diagnosis of myasthenia gravis was made again. When last heard from, in 1949, the patient was well and working regularly and no longer needed to take neostigmine.

CASE 4.—A man, aged 43 years, registered in April, 1949, at which time he complained of double vision which had occurred periodically for 10 months, slight shortness of breath at times, and some drooping of the right eyelid late in the day. The thyroid was diffusely enlarged, the skin was moist and warm, the blood pressure was 148/80, and the pulse rate varied from 88 to 96 per minute. A clinical diagnosis of hyperthyroidism was made. The basal metabolic rate was +30% and a radioactive iodine study revealed the following data for the tracer substance: thyroid fraction 76% of dose, accumulation rate 13.7% per hour, and renal excretion rate 4.2% per hour. A few days later the results of the radioactive iodine study were essentially unchanged. A curare test was performed, and it was shown that the man was extremely sensitive to 1/140 of a curarizing dose of the drug. A diagnosis of myasthenia gravis was made. A mild degree of ophthalmoplegia was present, and this did not respond particularly to the administration of neostigmine. The patient was treated with I^{131} and was seen for a check-up examination in October, 1949, at which time he was euthyroid. His complaints had disappeared.

CASE 5.—A woman, aged 29 years, registered at the clinic in August, 1951. She had been seen by her local physician in December, 1949, at which time her thyroid gland was enlarged and the basal metabolic rate was +59%. She had lost 20 lb. (9 kg.) and had tachycardia and excessive sweating and much nervousness. A mild exophthalmos was said to be present. She was treated with thiouracil, sedation, and rest in bed. One month after the inauguration of treatment a subtotal thyroidectomy was performed. In March, 1950, she had returned to her local physician complaining of double vision, with increasing exophthalmos of the right eye. The basal metabolic rate at that time was —3%, and the patient was given 6 grains (0.36 gm.) of thyroid daily without improvement. In July, 1950, she had complained of weakness, first in one arm and then in both arms, and the local physician gave her neostigmine but the result was difficult to interpret.

Examination after registration revealed severe exophthalmos, greater on the right than on the left. The patient appeared to be euthyroid. The basal metabolic rate was +3%. It was

also noted that there was a Grade 2 to 3 ophthalmoplegia. The patient was extremely sensitive to 1/140 of a curarizing dose of the drug, so that voluntary closing of the eyes became —3 to —4 bilaterally. Neostigmine treatment was started, with considerable improvement in the patient's local signs and general condition.

CASE 6.—A man, aged 23 years, registered at the clinic in September, 1944. He complained of the onset of weakness in 1938, with new features gradually being added through the years until a diagnosis of myasthenia gravis was made in March, 1944. In April of that year the patient received 10 roentgen treatments to the area of the thymus. When he was examined in September, 1944, there was weakness of the eyelids, some impairment of ocular rotation, and weakness of the muscles of mastication and of the upper extremities. There was a positive response to the administration of neostigmine. The basal metabolic rate was —13%. Roentgenograms of the chest revealed the presence of an anterior mediastinal mass, and thymectomy was performed on Sept. 15, 1944. The patient returned for a check-up examination in April, 1945, at which time he was very pleased with his clinical course and stated that he had been working full time and taking about one-half tablet of neostigmine twice a day. In June, 1950, there developed tachycardia, nervousness, and generalized weakness, a blood pressure of 160/90, and a basal metabolic rate of +15%. There was apparently no positive response to neostigmine. A thyroidectomy was performed in another institution in June, 1950, following which the patient rapidly regained his strength, no longer had shortness of breath, and felt normal.

CASE 7.—A woman, aged 41 years, registered in October, 1947. She had first noticed trouble in the early months of 1941, when ptosis of the right eyelid was noticed and there was some transient diplopia. Then she began to have trouble in walking, stubbing her toes easily and being unable to get up. Then further weakness and intolerance to heat developed; there was loss of weight and the pulse became very fast. In January, 1942, thyroidectomy had been performed, following which she was much improved. In May, 1943, diplopia had been again noted and ptosis returned. In September, 1947, a series of ulcers of the left cornea had developed and her eyes became immobile except for some lateral movement. She was unable to close the left eye completely, and there was mild bilateral exophthalmos. Following the administration of neostigmine there was definite improvement in her ability to use the eye muscles and she was able to close the eyelids completely. The basal metabolic rate at that time was —2%. Administration of neostigmine was continued. The patient was last heard from in 1949, at which time she was having practically no symptoms as long as her dose of neostigmine was carefully regulated.

CASE 8.—A woman, aged 21 years, registered in May, 1951. She had been well until 1947, when she had begun to have marked weakness, particularly in the lower extremities, nervousness, and tremor of the hands. The basal metabolic rate was +40%. She was being prepared for thyroidectomy when she began to complain she was falling frequently owing to severe weakness of the lower extremities. A neostigmine test was done, and there was considerable improvement, following which she began to take six to twelve 15 mg. tablets of neostigmine bromide per day. On Aug. 13, 1947, thyroidectomy was done, following which there was marked improvement in the nervousness and the weakness in the lower extremities during the winter of 1949 and 1950, so that the dose of neostigmine was reduced to approximately one to two tablets per day. From the spring of 1950 onward there had been an increase in the symptoms and the patient complained of double vision, slight ptosis, nasal speech, and occasional choking spells.

At the time of examination at the clinic in May, 1951, there was marked weakness of the facial musculature, of the tongue, and of the serratus anterior and some weakness of the biceps and triceps of both upper extremities and also some weakness in both hands. Roentgenograms of the chest showed no evidence of a thymic tumor. The weakness responded positively to the administration of neostigmine. The dose was regulated, and in addition the patient received ⅛ grain (0.024 gm.) of ephedrine sulfate three times a day. Nothing further is known of this patient.

CASE 9.—A woman, aged 39 years, registered at the clinic in November, 1939. She complained of loss of weight, trouble in sleeping, tiredness all the time, and depression. Her symptoms had been present for six months. In August, 1939, exophthalmos had been noted and the patient had been given strong iodine solution, U. S. P., 10 drops three times a day, and felt considerably improved. In October of the same year she had noticed that her facial muscles

felt weak and stiff and that her lips were flabby and without good muscle power. In November there was double vision and ptosis of the left eyelid, difficulty in chewing and swallowing, and a nasal twang to the speech. Her hands would get weak easily, so that she would drop a comb. There was loss of weight and progressive exophthalmos.

On examination at the clinic there were found weakness of the lips, some weakness of the eye muscles, evidence of loss of weight, pulse rate of 90 to 100, and a basal metabolic rate of + 21%. The patient had a definitely positive result of the neostigmine test, and a diagnosis of both hyperthyroidism and myasthenia gravis was made. Thyroidectomy was performed in December, 1939, following which the patient progressively improved, both as to nervousness and weakness, so that within six to nine months she no longer had to take neostigmine. She was then followed at intervals until 1946 and continued well with no need for neostigmine therapy. A careful examination was done in 1943, and no evidence of myasthenia gravis was detected, even following the administration of 1/5 of the curarizing dose of curare. Again, in 1946 there was no evidence of myasthenia gravis. A letter from the patient in 1951 stated that she was getting along well, continuing to run her business and take care of her house, and having no evidence of recurrence of her myasthenia gravis.

Case 10.—A woman, aged 33 years, registered in November, 1942, at which time she complained of double vision, some headache, nervousness, and palpitation, which had occurred off and on for eight years. On examination there was warm moist skin, tremor of the outstretched hands, diffuse enlargement of the thyroid gland, and weakness of the extraocular muscles so that there was a mild ophthalmoplegia and mild ptosis. A clinical diagnosis of hyperthyroidism and myasthenia gravis was made. Following administration of quinine there was worsening of the eye muscle movement so that the function of the right lateral rectus became —4. This was markedly improved by the administration of neostigmine. The basal metabolic rate was + 35%, and following neostigmine treatment and 10 drops of strong iodine solution, U. S. P., three times a day there was marked improvement.

Case 11.—A woman, aged 39 years, registered in September, 1946. At that time she complained of great difficulty in eating (because of weakness), trouble in talking, and double vision. There was also weakness of the hands and arms. The positive history began in 1941, when there had been difficulty with speech. A diagnosis of myasthenia gravis had been made in 1943, and the patient had been under treatment with neostigmine from that time until registration at the clinic. Physical examination revealed evidence of marked loss of weight; warm moist hands, with tremor of the outstretched hands; a pulse rate of 120, and blood pressure of 110/70. The basal metabolic rate was + 21%. A diagnosis of hyperthyroidism and myasthenia gravis was made. Roentgenograms of the chest revealed a mass in the anterior mediastinum. The patient entered the hospital, where the dose of neostigmine was regulated, but the principal problem was the difficulty of getting her to ingest an adequate diet because of the great difficulty in swallowing. The patient left Rochester, and word was received that she had died on Nov. 24, 1946.

Case 12.—A woman, aged 58 years, registered in June, 1943. She had been well until July, 1940, when she began to have difficulty in swallowing and fluid regurgitated through her nose when she attempted to swallow. There was gradual improvement until 1943, when an elevated blood pressure was noted and there was tiring of the voice, worse in the evening than at other times. In May, 1943, she began to have great difficulty in swallowing, trouble in chewing, weakness of the arms and legs, and mild ptosis. Physical examination at the clinic revealed Grade 3 ptosis bilaterally, and Grade 3 weakness of the masseter muscles, temporal muscles, all the facial muscles, and the muscles of the neck. There was weakness of the biceps brachii, Grade 2, and of the iliopsoas, quadriceps, and to a lesser degree the muscles throughout both lower extremities. The basal metabolic rate was + 56% and on another occasion + 59%. Eventually there was marked improvement following the administration of neostigmine, and a diagnosis of hyperthyroidism and myasthenia gravis was made. The pulse rate at that time was 120 per minute, and the blood pressure was 198/104. Roentgenograms of the chest showed no abnormalities. The patient was hospitalized; neostigmine was administered, and treatment with strong iodine solution, U. S. P., and thiouracil was initiated. The patient's progress was poor, and she died on July 14, 1943.

Case 13.—A woman, aged 32 years, registered at the clinic in January, 1947. She had been well until 1943, when double vision and a palsy of the right external rectus muscle developed.

In 1945 she began to have weakness of the grip and her speech became thick after talking for awhile. A diagnosis of myasthenia gravis was made in March, 1946, and neostigmine treatment was started. In June, 1946, she noted nervousness and intolerance to heat. Basal metabolic rates, determined in June, 1946, by a local physician, were + 25 and + 39%. A record of a basal metabolic rate done in 1939 was —6%.

When the patient was examined at the clinic there was palsy of the right lateral rectus muscle, weakness of the neck, and Grade *2* weakness of the deltoids, iliopsoas, and hamstring muscles. The pulse rate was 120. The blood pressure was 118/66, and the basal metabolic rate was + 52% on one occasion and + 48% on another occasion. Roentgenograms of the chest showed no abnormalities. There was definite response to neostigmine, and a diagnosis of hyperthyroidism and myasthenia gravis was made. Treatment was started with strong iodine solution, U. S. P., and neostigmine. The patient returned home, and word was received that she had died in November, 1947, when a thymectomy was attempted at another institution.

CASE 14.—A woman, aged 67 years, registered at the clinic in 1947. In 1927 she had complained of great nervousness and loss of weight, and following a metabolism test had been told that she suffered from hyperthyroidism. A thyroidectomy was performed. In 1928 drooping eyelids had developed and she had had difficulty in moving the eyeballs. Shortly thereafter there was weakness of the arms, so that she could not do anything in the way of work around the house and her speech was very poor because of weakness. These symptoms improved gradually during 1929 and 1930. Some ptosis continued, and when she was examined at the clinic in 1947 there was inability to move the right eye upward and inability to move the left eye to the left, Grade 3 weakness of the triceps muscles, and 3 + ptosis bilaterally. These weaknesses were improved by neostigmine, but the eye muscle functions did not return to normal. A program of neostigmine therapy was arranged for her. Word was received from her in 1947, at which time she was so improved that she did not have to take neostigmine.

CASE 15.—A man, aged 57 years, registered at the clinic in June, 1935. For the preceding six months he had noted increasing difficulty in chewing due to weakness of the jaw muscles. Shortly after the onset of this trouble he had noted generalized muscular weakness, particularly in both upper extremities. There was occasional difficulty in swallowing. On examination the pulse rate for 104 and was totally irregular (auricular fibrillation). The blood pressure was 136/72, and there was a systolic murmur over the sternum, with a systolic and diastolic murmur over the aortic area. There was definite diffuse enlargement of the thyroid gland. There were muscular weakness of the jaw and some difficulty in swallowing. The basal metabolic rate was + 19%. A diagnosis of hyperthyroidism and myasthenia gravis was made, and treatment with strong iodine solution, U. S. P., was started. On a number of occasions during the next two years the patient was examined at the clinic. There was evidence that the thyroid hyperactivity had quieted, and the pulse rate gradually returned to normal. The basal metabolic rate dropped to + 10%. The myasthenia gravis gradually progressed in severity until the chest musculature was involved, and the patient died in respiratory failure Oct. 9, 1937.

CASE 16.—A man, aged 22 years, registered at the clinic in June, 1942. In 1937 extreme nervousness, exophthalmos, and loss of weight had developed. A thyroidectomy was performed, following which the nervousness disappeared; the patient gained weight but the exophthalmos did not change. In the spring of 1941 he noted loss of strength, especially in the arms and hands, which was worse in the afternoon and evening than at other times. He was unable to whistle because he tired so easily and had trouble in chewing, likewise because of tiring. Physical examination revealed a mild exophthalmos, 1 + slurring of the speech, and Grade *2* impairment of eye closing. Following administration of quinine there was marked increase in the weakness, so that the patient could not walk on his heels and could not rise from a squatting position. The deltoids were weak, Grade 3. Administration of neostigmine produced great improvement, and a diagnosis of myasthenia gravis was made. The patient was regulated on doses of neostigmine bromide. At that time the basal metabolic rate was + 5%, and the roentgenograms of the chest showed no abnormalities. The patient has continued in about this same condition since that time, with neostigmine continuing to give marked relief from the weakness.

CASE 17.—A woman, aged *27* years, was first seen at the clinic in April, 1943, at which time she complained of double vision which had been present off and on for four years. It

had begun one month after thyroidectomy for symptoms of nervousness, loss of weight, and diffuse weakness. At the time of examination at the clinic there were ptosis, double vision, and weakness of the neck, all of which were made much worse by the administration of quinine. Response to neostigmine was definite, and a diagnosis of former hyperthyroidism with myasthenia gravis was made. The basal metabolic rate was —10%. Roentgenograms of the chest showed no abnormalities. Treatment with neostigmine was outlined, and the patient was last heard from in December, 1943, at which time she was getting along fairly well while taking the drug.

Case 18.—A woman, aged 56 years, registered at the clinic in February, 1945. She related that in 1940 she had begun to notice weakness and inability to move her eyeballs. There were ptosis of the left eyelid and weakness of the right hand off and on until 1945. At the time she was examined at the clinic the blood pressure was 180/104; the pulse rate was 106. the thyroid was slightly enlarged, and there was marked weakness of the facial musculature, with eyelid closing —3 to —4/—3 to —4, neck weakness, and upper extremity weakness Grade 1 to 2 bilaterally. There was iliopsoas and quadriceps weakness on both sides in the lower

Fig. 1 (Case 19).—Hyperthyroidism (exophthalmos) and myasthenia gravis (ptosis in right eye). (*a*) before neostigmine; (*b*) after neostigmine.

extremities. The patient was treated with strong iodine solution, U. S .P., and roentgen therapy to the thyroid and to the thymus. There was definite response of the weakness of iliopsoas and quadriceps muscles to neostigmine, and a diagnosis of hyperthyroidism and myasthenia gravis was made. The patient was instructed concerning the use of neostigmine and when last checked in 1950 was getting along fairly well. Her basal metabolic rate was + 21%, and she was continuing to take daily doses of neostigmine and strong iodine solution, U. S. P.

Case 19.—A woman, aged 42 years, registered in December, 1941. A thyroidectomy had been performed in August, 1937, for nervousness, loss of weight, and exophthalmos. She had then been well until 1939, when her left eye began to bulge further and this became gradually more severe. Her local physician prescribed strong iodine solution, U. S. P. In 1940 she had noted weakness of inward and downward gaze in the left eye and there was increasing bulging of the right eye. She complained that there was weakness in the arms when she played the piano. In 1941 weakness of the legs developed, particularly after exercise. Physical examination revealed a Grade 3 exophthalmos bilaterally, ptosis of both lids, weakness of the lateral and inferior rectus muscles in both eyes, and a palpable thyroid gland. Her blood pressure was 120/70, and the pulse rate was 80 per minute. The basal metabolic rate was + 4%. It was agreed that the patient was essentially euthyroid. A neostigmine test was done (Fig. 1).

There was a definite response in the iliopsoas muscles, and a diagnosis of myasthenia gravis was made. The eye muscle response to neostigmine was poor. Roentgen therapy to the thymus was given. The patient was seen again in March, 1943, at which time there was shortness of breath; weakness of the chest musculature; severe weakness in the legs, upper extremities, and eye muscle movements, and ptosis. The patient was put in a respirator March 29, 1943, and died on March 30, 1943, without having responded at all well to neostigmine treatment.

CASE 20.—A woman, aged 19 years, registered in September, 1943. She related that in 1941 she had begun to talk indistinctly with a nasal twang to her speech. Shortly thereafter she had noted difficulty in swallowing, and in January, 1942, she had begun to have trouble using her hands. In March of that year her arms had begun to give way because of weakness. In June, 1942, she had had coughing attacks because of difficulty in swallowing, and in November, 1942, a diagnosis of myasthenia gravis was made by her local physician. Neostigmine treatment was started. In January, 1943, there had been more difficulty with swallowing and trouble in breathing, and in September of that year she had begun to have drooping of the eyelids.

On examination at the clinic there was found weakness throughout the motor cranial nerves, upper extremities, and lower extremities. The blood pressure was 114/78, pulse rate was 108 per minute, and the basal metabolic rates were + 28 and + 19%. There was a definite response to neostigmine, and a diagnosis of hyperthyroidism and myasthenia gravis was made. Roentgenograms of the chest showed no abnormalities. A program of neostigmine therapy was outlined, and the patient was last heard from in 1949, at which time she was getting along quite well taking five or six neostigmine tablets a day. Apparently there had been some decrease in the quantity of thyroid activity.

CASE 21.—A woman, aged 56 years, registered in July, 1938. In 1930 she had noted difficulty in chewing hard objects, and in 1932 there had been trouble with speech because of weakness. In 1933 there had been difficulty with swallowing, and water came back through her nose on a number of occasions when she attempted to swallow it. These symptoms had improved, but in late 1937 there had been a return of the speech difficulty; it was almost impossible for her to close her jaws and she noted ptosis of both eyelids.

On physical examination there were found ptosis, some impairment of ocular rotation, a Grade 3 to 4 weakness of the muscles of mastication, difficulty in swallowing, substernal enlargement of the thyroid gland, blood pressure of 168/84, and a pulse rate of 118 per minute. The basal metabolic rate was + 62%. There was also definite weakness of both upper extremities and both lower extremities. There was a definite response to neostigmine, and a diagnosis of hyperthyroidism and myasthenia gravis was made. A program of neostigmine therapy was outlined, and strong iodine solution, U. S. P., was prescribed. The patient did not return to the clinic, but word was received that she had died later in 1938.

CASE 22.—A woman, aged 58 years, was first seen at the clinic in April, 1945. She had undergone thyroidectomy in 1918 because of nervousness, loss of weight, weakness, trembling of the hands, and a marked increase in pulse rate, with an additional notation that the thyroid gland was enlarged. At the time she was examined in 1945, the basal metabolic rate was + 9% and there were bilateral ptosis; some impairment of ocular rotation, and weakness of the facial muscles, upper extremities and lower extremities, all of which responded definitely to neostigmine treatment. A program of neostigmine therapy was outlined, with which the patient did fairly well until 1949, when she gradually became worse. Corticotropin (ACTH) was administered in a dose of 100 mg. per day for 14 days, during which time there was slight worsening of the patient's condition, followed by a return of her condition to the premedication state. Word was received that the patient had died Feb. 3, 1952, apparently as a result of myasthenia gravis.

CASE 23.—A man, aged 35 years, registered in March, 1947. He had undergone thyroidectomy in 1937 and, again, in 1941 for nervousness, loss of weight, increased pulse rate, and a basal metabolic rate of + 50%. He was well until June, 1946, when he noticed weakness of the extensors of the thighs and he was unable to climb up onto the tractor or out of a chair. There was progressive weakness of the lower extremities from that time onward. In October, 1946, both feet had begun to drag. On physical examination there was found Grade 2 weakness throughout both lower extremities, with a definite response to neostigmine. A diagnosis of former hyperthyroidism and myasthenia gravis was made. The patient ultimately

underwent thymectomy and he was last heard from rather recently, when he was still taking a small amount of neostigmine and getting along well.

CASE 24.—A woman, aged 56 years, registered at the clinic in December, 1949, at which time she gave a history of having undergone thyroidectomy in 1918 for weakness, loss of weight, fast pulse, and mild exophthalmos. In 1946 she had complained of double vision, ptosis, and weakness of the neck. On examination there was found impaired movement of the left inferior rectus and some weakness of the left lateral rectus muscle. There was also weakness of the right internal rectus muscle. These muscle weaknesses were markedly improved by the administration of neostigmine. The basal metabolic rate was —10%. The patient has received thyroid medication off and on during the last few years, but it seems to make little difference in her condition. The dose of neostigmine was regulated, and she has got along quite well up to and including 1952.

CASE 25.—A woman, aged 68 years, registered at the clinic in May, 1943. She complained of having had a goiter for about 50 years and a progressive weakness for approximately six to eight weeks, the voice, eyelids, tongue, and swallowing muscles being involved so severely that two weeks before registration she began to have difficulty with fluid regurgitating through her nose. On physical examination there were found a nodular enlargement of the thyroid gland, difficulty in speaking, and marked difficulty in swallowing. The blood pressure was 160/85, and the pulse rate was 94 per minute. There were slight ptosis bilaterally and marked involvement of the facial musculature, the tongue strength being —2. There was a definitely positive response to neostigmine, and the basal metabolic rate was + 20%. A diagnosis of hyperthyroidism and myasthenia gravis was made. Roentgenograms of the chest showed no abnormalities. The patient's condition was regulated with neostigmine, and a thyroidectomy was ultimately performed, following which the patient died.

COMMENT CONCERNING CASES

Case 2 illustrates the need, in certain instances, for the use of tests other than the administration of neostigmine to establish a diagnosis of myasthenia gravis. The development of a unilateral partial ptosis, while the patient was under observation, was an indication for performing the curare test, which established the diagnosis of myasthenia gravis.

Case 3 is an example of the variability in the natural history of myasthenia gravis. Remission occurred six years after thyroidectomy. Thyroid was administered, but available evidence does not indicate a constant relationship between administration of this hormone and amelioration of the myasthenia. Case 14 is also one in which spontaneous remission occurred, without thymectomy or administration of thyroid or corticotropin.

In Cases 5, 7, and 19 the patients were euthyroid and had been so for a number of years when myasthenia gravis developed. In the first and last instance there was definite exophthalmos, which likewise developed while thyroid function was normal. Neither the exophthalmos nor ophthalmoplegia was improved by the administration of thyroid, but the ophthalmoplegia responded to neostigmine. In Case 7 the patient had severe ophthalmoplegia, mild exophthalmos, and severe peripheral weakness of myasthenia. In this instance both the ophthalmoplegia and the peripheral weakness responded to neostigmine therapy.

In Cases 22 and 23, also, hyperthyroidism was successfully treated a number of years before the first symptoms of myasthenia gravis appeared.

Case 6 was of unusual interest. Myasthenia gravis appeared in a euthyroid person. Thymectomy was performed. The myasthenia gravis gradually disappeared. Then hyperthyroidism appeared, but the symptoms of myasthenia gravis did not recur.

Case 9 is a remarkable example of simultaneous development of hyperthyroidism and myasthenia gravis, with cure of the hyperthyroidism by thyroidectomy and simultaneous remission of the myasthenia gravis. In contrast, in Case 15 the symptoms of myasthenia increased in severity as the hyperthyroidism abated. Another variation of the relationship of the two disorders is illustrated in Case 21. Myasthenia gravis began and gradually became more severe for eight years. Hyperthyroidism then developed, as though superimposed on the natural course of the myasthenia, and the patient died a few months later.

GENERAL COMMENT

Clinical experience and pharmacologic evidence indicate that myasthenia gravis and hyperthyroidism, as they are known today, are separate diseases. Weakness of the muscles supplied by the trigeminal, facial, glossopharyngeal, and vagus nerves and by the third cranial nerves in the absence of exophthalmos is common in myasthenia gravis and practically nonexistent in hyperthyroidism. The physical signs of hyperthyroidism are not commonly seen in myasthenia gravis. The administration of neostigmine does not significantly change the weakness of hyperthyroidism,[13] whereas most patients with myasthenia gravis have the weakness greatly lessened by the correct use of neostigmine. There are exceptions to the latter statement. Patients with advanced myasthenia gravis may have weakness which responds slightly, if at all, to neostigmine. In addition, there are some instances in which certain myasthenic muscles respond well to administration of neostigmine while other weak muscles, in the same patient, do not respond.[14] The ophthalmoplegia of myasthenia gravis is an example of a site of weakness which may remain little changed by test doses of neostigmine, although the patient has classic myasthenia gravis. Another distinction between the two diseases is seen in the difference in response of each one to the administration of curare. McCorkle[15] has studied the reaction to the injection of *d*-tubocurarine of 20 patients with severe hyperthyroidism. These patients did not have clinical evidence of myasthenia gravis. In no instance was there increased sensitivity to the drug as compared to the response in a group of normal persons. Two of the 20 patients had exophthalmos with ophthalmoplegia. The abnormal sensitivity to curare of patients with myasthenia gravis is well known.[16] It would appear that the weakness of hyperthyroid patients is not due to a defect of transmission of nerve impulses, but the pathogenesis of the altered physiology, clinically expressed as weakness in muscle contraction, is not understood at this time.

Table 1 details the sequence of development of hyperthyroidism and myasthenia gravis. In 68% of the cases the hyperthyroidism came before or simultaneously with the myasthenia gravis. In 12%, however, there was an interval of more than

13. Schwab, R. S., and Chapman, W. P.: Clinical Uses of Neostigmine, M. Clin. North America **31**:1238-1260 (Sept.) 1947.

14. See case noted earlier in this paper.

15. McCorkle, J. K.: Myasthenia Gravis and Exophthalmic Goiter: Being a Study of Certain Possible Interrelationships Between the 2, Thesis, University of Minnesota Graduate School, 1952.

16. Bennett, A. E., and Cash, P. T.: Myasthenia Gravis: Curare Sensitivity; a New Diagnostic Test and Approach to Causation, Arch. Neurol. & Psychiat. **49**:537-547 (April) 1943. Eaton, L. M.: The Clinical Concept of Myasthenia Gravis, Proc. Staff Meet., Mayo Clin. **23**:1-7 (Jan. 7) 1948.

five years, and if only those cases are listed in which the interval was short the figure is changed to 36%. McCorkle's summary of 20 cases reported since the advent of neostigmine therapy shows that 15 (75%) had hyperthyroidism first or the simultaneous onset of the two diseases. If there is special significance to these observations, it is not apparent.

In our experience the incidence of hyperthyroidism before, during, or after detectable myasthenia gravis has been about 5%. A reciprocal relationship does not exist; that is, only a fraction of 1% of patients with hyperthyroidism ever have myasthenia gravis. Our experience does not correspond with that of McEachern and Parnell [9] and of Thorner,[7] who noted a "see-saw" relationship of a "physiologic antagonism" between the two diseases. Progression of myasthenia gravis with lessening of hyperthyroidism has been noted (Case 15), but this relationship has been uncommon and does not appear to be of special significance. In Cases 5 and 19 exophthalmos, ophthalmoplegia, and myasthenia gravis developed after thyroidectomy and while the patient was euthyroid, but evidence for drawing any special conclusion from this sequence of events is tenuous indeed. It is true that one physical finding, ophthalmoplegia, occurs with considerable frequency in both diseases. In hyperthyroidism the ophthalmoplegia is sometimes not easily explained

TABLE 1.—*Sequence of Development of Hyperthyroidism and Myasthenia Gravis*

	Cases, No.	%
Hyperthyroidism first	9	36
Myasthenia gravis first	8	32
Simultaneous onset	2	8
Simultaneous ?	3	12
Hyperthyroidism first, but more than 5 yr. apart	3	12

by the presence of exophthalmos, which may be mild even though the ophthalmoplegia is severe, and in myasthenia gravis the ophthalmoplegia is sometimes little affected by the administration of neostigmine or curare. While it has long been postulated that a special fraction of pituitary secretion is responsible for this phenomenon in patients who have had hyperthyroidism, there is no evidence to link this postulate to the pathogenesis of myasthenia gravis nor is there factual evidence that a pituitary product is solely responsible for exophthalmos of Graves' disease.

Cohen and King [6] and McCorkle [15] have commented concerning the hyperplasia of lymphoid tissue which may occur in the two diseases, but this observation has thus far failed to lead to a practical explanation of the pathogenesis of the two disorders. Further fruitful investigation is needed to explain the occurrence of these two diseases in the same patient. It continues to appear that their relationship in this manner is outside the statistical possibility of a chance occurrence.

That treatment of these two disorders has not been satisfactory is evident. Of the 25 patients reported, 10 died, a mortality rate of 40%. Table 2 shows that the deaths were directly attributable to the muscle weakness associated with myasthenia gravis. How much this muscle weakness was made worse by the coexistence of hyperthyroidism could not be determined in any single patient at any given time. Hyperthyroidism in itself can produce much weakness. It is altogether possible that it can add its own effect to that of myasthenia gravis, the total result being greater than that produced by either disease. Treatment is, therefore, aimed at reducing the abnormality characteristic of each disease. Thyroidectomy is unusually

TABLE 2.—*Data on Patients Who Had Hyperthyroidism and Myasthenia Gravis*

Case	Sex	Age, Yr.	Cranial Nerve Involvement	Ophthalmoplegia	Peripheral Weakness	Ophthalmoplegia, Neostigmine Response	Other Neostigmine Response	Exophthalmos	Pulse Rate/Min.	B. P.	Thyroid Enlarged	B. M. R.	Thymus Detectable	Treatment	Died of Myasthenia Gravis	Sequence of Development of Diseases: Hyperthyroidism First	Sequence of Development of Diseases: Myasthenia Gravis First	Sequence of Development of Diseases: Simultaneous
1	F	43	+	..	+	..	+	..	138	160/60	+	+43	..	Thyroidectomy* Thiouracil, neostigmine	+	+	..	..
2	F	63	+	..	+	..	+	..	80	150/80	..	+26	+	S. I.,† neostigmine, etc.	+	..	..	+?
3	F	19	+	+	..	..	+	..	110	120/80	..	+26	..	Thyroidectomy, neostigmine	..	..	+	..
4	M	43	+	+	..	..	+	..	96	150/80	+	+30	..	I^{131}, neostigmine	..	..	..	+
5	F	29	..	+	+	..	+	+	104	160/90	..	+59	+	Thyroidectomy, neostigmine	..	+	..	..
6	M	23	+	+	+	..	+	..	100	160/90	..	+15	+	Thyroidectomy* Thymectomy, neostigmine	..	..	+	..
7	F	41	+	+	+	+	+	+	120	130/75	..	?	..	Thyroidectomy* Neostigmine, etc.	..	+	..	..
8	F	21	..	+	+	..	+	..	100	140/50	+	+40	..	Thyroidectomy, neostigmine	..	+	..	..
9	F	39	+	+	..	+	+	+	100	150/80	+	+21	..	S. I., thyroidectomy, neostigmine	..	+	..	..
10	F	33	+	+	..	+	+	..	96	130/80	..	+35	..	S. I., neostigmine	..	..	..	+?
11	F	39	+	+	+	+	+	..	120	110/70	+	+21	+	S. I., neostigmine	+	..	+	..
12	F	58	+	..	+	..	+	..	120	180/110	+	+59	..	S. I., thiouracil, neostigmine	+	..	+	..
13	F	32	+	+	+	±	+	..	120	120/65	±	+52	..	S. I., neostigmine Thymectomy*	+	..	+	..
14	F	67	+	+	+	..	+	..	84	150/85	..	+50*	..	Thyroidectomy* Neostigmine	..	+	..	..
15	M	57	+	..	+	..	+	..	104	136/72	+	+19	..	S. I., neostigmine	+	..	..	+
16	M	22	+	..	+	..	+	+	80	130/85	..	+5	..	Thyroidectomy* Neostigmine	..	+	..	..
17	F	27	+	+	..	+	+	+	80	130/90	..	−10	..	Thyroidectomy* Neostigmine	..	+	..	..
18	F	56	+	+	+	±	+	..	106	180/104	+	?	..	S. I., neostigmine, x-ray to thymus	..	..	+	..
19	F	42	+	+	+	±	+	+	80	120/80	..	+4	..	Thyroidectomy* S. I., neostigmine	+	+	..	..
20	F	19	+	..	+	..	+	..	108	115/80	±	+28	..	Neostigmine, x-ray to thymus	..	..	+	..
21	F	56	+	..	+	..	+	..	118	170/85	+	+62	..	S. I., neostigmine	+	..	+	..
22	F	58	+	+	+	..	+	..	76	140/80	..	+9	..	Thyroidectomy* Neostigmine, corticotropin	+	+	..	..
23	M	35	..	..	+	..	+	..	72	135/85	..	+50*	+	Thyroidectomy, 2X* Thymectomy, neostigmine	..	+	..	..
24	F	56	+	+	..	±	+	..	88	140/90	..	−10	..	Thyroidectomy* Neostigmine	..	+	..	..
25	F	68	+	..	..	..	+	..	94	160/85	+	+20	..	Thyroidectomy, neostigmine	+	..	..	+?

* Done elsewhere.
† S. I. = stron iodine solution, U. S. P.

hazardous in the presence of trouble in swallowing, coughing, and breathing. In certain instances the administration of strong iodine solution, U. S. P., or thiouracil or both did not control the hyperthyroidism. In others the weakness was so great that the risk of thyroidectomy was prohibitive. Now that I^{131} is available for treatment, control of the hyperthyroidism can be attacked with less danger than before this therapeutic agent was developed (see Case 4). While new drugs such as octomethyl pyrophosphoramide and tetraethylpyrophosphate and hormones such as cortisone and corticotropin are being used, our experience points to some form of therapy with neostigmine as the most reliable means of sustaining patients who have myasthenia gravis. This is particularly true when the muscle weakness is severe and widespread. Treatment, therefore, consists of a combination of the most modern therapies for each of the two diseases.

THYROTOXIC MYOPATHY

The term "thyrotoxic myopathy" or "chronic thyrotoxic myopathy" has gradually entered medical literature during the last 15 years. A brief review of this subject reveals that there is some difference of opinion concerning the diagnosis and the frequency of occurrence of this disorder. The latter probably is a product of the former.

The difficulty in differential diagnosis centers around the following situations: chronic thyrotoxic myopathy, hyperthyroidism occurring simultaneously with myasthenia gravis, certain cases of muscular dystrophy, an entity which for want of a better term will be referred to as "myositis," and, finally, the matter of quantity of muscle wasting or weakness or both necessary before the term "myopathy" is used. McEachern and Ross [17] reported data on a patient who had hyperthyroidism and great weakness. The electromyogram revealed a defect similar to that observed in myasthenia gravis, and the hypodermic administration of 1.0 mg. of neostigmine methylsulfate produced "great improvement" in the weakness. A curare test was not done. It was concluded that there was no evidence of myasthenia gravis. Another patient on whom data were reported by the same authors had generalized weakness and loss of 17 lb. (7.7 kg.) but no evidence of muscle wasting or of selective decrease in the strength of any particular group of muscles. This case was cited as an example of "chronic thyrotoxic myopathy." The fifth patient described by Thorn and Eder [18] had generalized weakness and no muscle wasting. The neostigmine and curare tests and electromyogram were not done. The third patient cited by Morgan and Williams [19] died of respiratory paralysis on the 11th day after admission. No report is recorded concerning a cerebrospinal fluid examination or a neostigmine test. Quinn and Worcester [20] found only 19 cases of "chronic thyrotoxic myopathy" in the literature when they reported a case in 1951.

In an attempt to aid in defining "chronic thyrotoxic myopathy" and its diagnosis, data on the following cases are presented.

17. McEachern, D., and Ross, W. D.: Chronic Thyrotoxic Myopathy: A Report of 3 Cases with a Review of Previously Reported Cases, Brain **65**:181-192 (June) 1942.

18. Thorn, G. W., and Eder, H. A.: Studies on Chronic Thyrotoxic Myopathy, Am. J. Med. **1**:583-601 (Dec.) 1946.

19. Morgan, H. J., and Williams, R. H.: Muscular Atrophy and Weakness in Thyrotoxicosis (Thyrotoxic Myopathy; Exophthalmic Ophthalmoplegia), South. M. J. **33**:261-268 (March) 1940.

20. Quinn, E. L., and Worcester, R. L.: Chronic Thyrotoxic Myopathy: Report of a Case, J. Clin. Endocrinol. **11**:1564-1571 (Dec.) 1951.

REPORT OF CASES

Myositis

Case 26.—A woman, aged 26 years, registered at the clinic in August, 1952. She complained of weakness of the arms and legs, which had been present for a year. This had been first observed when she played the piano and progressed until she was unable to comb her hair because of inability to lift her arms into the air. There was considerable "nervousness" and shaking of the hands. Her appetite was good, but she had lost 10 lb. (4.5 kg.) in the preceding

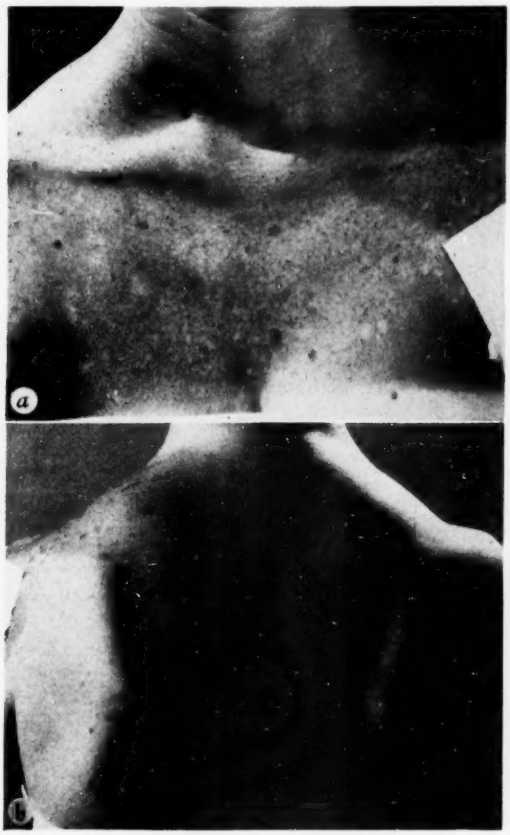

Fig. 2 (Case 26).—Shoulder girdle atrophy in patient with "myositis." Note the hollowing out of the deltoid area.

four months. There was intolerance to heat. Physical examination revealed fine tremor of the hands, which were warm and moist. There was Grade 2 weakness of eyelid-closing, trapezius, supraspinatus and infraspinatus, elbow flexor, quadriceps femoris, and thigh abductor muscles. There was Grade 3 weakness of the deltoids, pectoral muscles, triceps, wrist flexors, iliopsoas, and hamstrings. The blood pressure was 120/85, and the pulse rate was 96 per minute. The muscle stretch reflexes were markedly diminished or absent. There was 2 to 3 + shoulder girdle atrophy (Fig. 2). Urinalysis showed no abnormality, and white blood count was normal. The blood hemoglobin was 11.8 mg. per 100 cc. The differential blood count and Kline reaction were normal. The blood sedimentation rate was 6 mm. in one hour and 12 mm. in one hour

on another occasion. The result of the plasma L. E. test was negative for L. E. cells. Roentgenograms of the chest showed no abnormalities. Radioiodine study following a dose of 10 μc was reported as follows: 48-hour urinary excretion 63.8%, extrarenal disposal rate 6.5% per hour, 24-hour accumulation in thyroid 34.9%, accumulation rate 4.9% per hour, and renal excretion rate 7.1% per hour. The protein-bound blood iodine was 7.5 γ per 100 cc. Dr. Lambert's study with the electromyogram showed 2+ fibrillation in the left biceps brachii and 1+ in the deltoid muscles. There were no fasciculations. In the left biceps brachii, right triceps, and both deltoids the motor unit potentials were predominantly of low amplitude, with many sharp spike and polyphasic potentials present. Dr. Lambert interpreted the electromyogram as being compatible with a disorder of muscle and favored a diagnosis of myositis. A specimen for biopsy was obtained from the left deltoid muscle (Fig. 3). On gross examination the deltoid muscle was found to be atrophic.

Thyrotoxic Myopathy

Case 27.—A man, aged 55 years, was first seen in January, 1952, at which time he complained of loss of weight, of 38 lb. (17 kg.); hoarseness; double vision, and severe weakness of his legs. The symptoms had been gradually progressive for nine months. The abnormal physical signs were Grade 1 to 2 exophthalmos with partial ophthalmoplegia (greatest weakness was in the superior rectus muscles), warm moist hands, enlarged thyroid gland, 2 to 3+ wasting and weakness of the shoulder girdle muscles, tremor of the hands, and 2+ weakness and wasting of the muscles of the pelvic girdle and lower extremity (Fig. 4). The pulse rate was 96 per minute and regular. The basal metabolic rate was +32%. Roentgenograms of the chest showed no abnormalities. A radioiodine study revealed the following data (dose 300 μc): urinary excretion 14.0%, extrarenal disposal rate 12.3% per hour, 24-hour accumulation in thyroid 92.8%, accumulation rate 13.5% per hour, and renal excretion rate 2.0% per hour. The protein-bound blood iodine was 10.0 γ per 100 cc. Electromyographic examination was conducted by Dr. Lambert. There were no fasciculations or fibrillations, and the motor unit potentials were normal. There were no sharp spike or polyphasic potentials. (The biceps, triceps, deltoids, anterior tibial and quadriceps muscles were tested.) Dr. Lambert interpreted these observations as showing no evidence of denervation or of intrinsic muscle disease. A specimen for biopsy was obtained from the left biceps muscle. Study of the sections of this tissue demonstrated no significant abnormality (Fig. 5). One fifth of a curarizing dose of *d*-tubocurarine was injected intravenously, without producing any change in the patient's weakness. The patient was treated with I^{131}. Three months later he had gained 28 lb. (12.6 kg.) and his strength was essentially normal except for the ophthalmoplegia, which was unchanged.

Case 28.—A man, aged 66 years, was first seen in August, 1950, at which time he complained of loss of weight and marked weakness, particularly in his lower extremities. The latter was most apparent when he would go up and down steps, get up out of a low chair, or try to rise from kneeling on the floor. He had lost 45 lb. (20.25 kg.). On physical examination there was found 1 to 2 + wasting and weakness of the shoulder girdle muscles and 2+ wasting and weakness of the pelvic girdle muscles. There was 1+ wasting and weakness of the muscles of the forearm and the hands. The stretch reflexes were essentially normal. The pulse rate was 120 per minute. The basal metabolic rate was + 36% and the protein-bound blood iodine was 14.7 γ per 100 cc. In a radioactive iodine study, after the injection of 100 μc of the substance, the following values were obtained: thyroid fraction 72.6% of the dose, accumulation rate 22.6% per hour, and renal excretion rate 1.3% per hour. The patient was treated with I^{131}. He was last seen for a checkup examination in May, 1952, at which time muscle function and size were normal and he was euthyroid.

Case 29.—A man, aged 31 years, registered at the clinic in December, 1949, at which time he complained of having had loss of weight over a five-month period and increasing weakness for three months, particularly in the shoulder girdle muscles. On physical examination there was found 1 to 2+ wasting and weakness of the shoulder girdle muscles, while the results of the remainder of the muscle tests showed no abnormalities. The stretch reflexes were slightly hyperactive. There had been a loss of 36 lb. (16.2 kg.). The thyroid gland was slightly enlarged, and there was a nodule with a diameter of 1 cm. in the medial portion of

the right lobe. The pulse rate was 110 and regular, and the basal metabolic rate was +51%. Roentgenograms of the chest showed no abnormalities, and there was no increase in strength following administration of neostigmine methylsulfate. The result of the curare test was normal. Thyroidectomy was performed Dec. 30, 1949, and in May, 1950, word was received from the patient that muscle function and weight had apparently returned to normal.

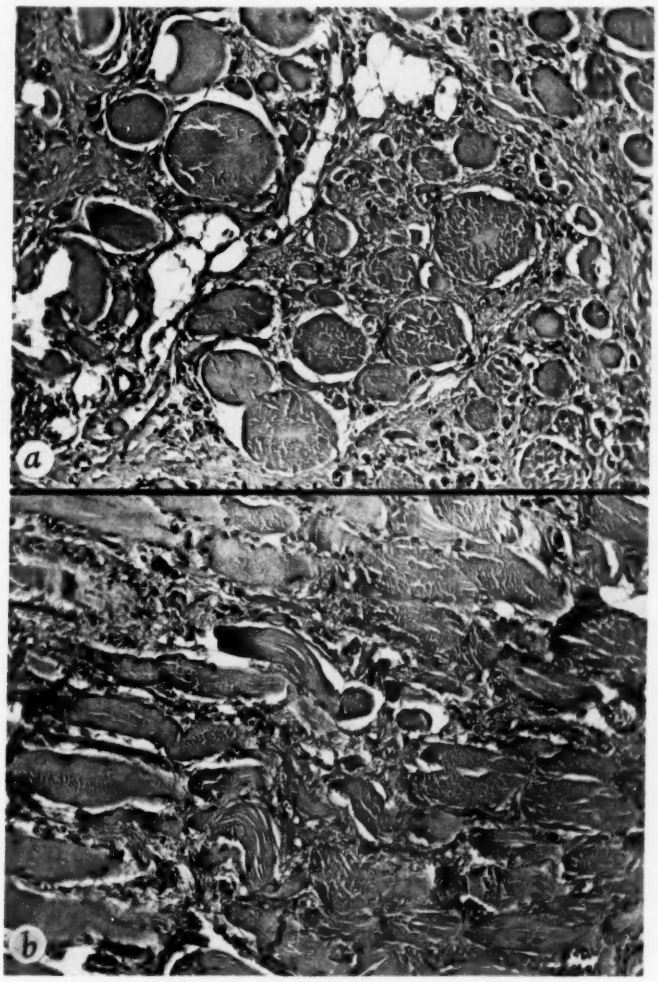

Fig. 3 (Case 26).—Specimen for biopsy taken from the left deltoid muscle. There is mild to marked degeneration of muscle fibers and collections of round cells in the interstitial tissue. Hematoxylin and eosin; (*a*) × 115, (*b*) × 125.

CASE 30.—A woman, aged 50 years, was first seen in September, 1948, at which time she complained of having had nervousness for six years, a loss of 40 lb. (18 kg.) in four months, and severe muscular weakness, particularly in the lower extremities. There had been some tremor and mild intolerance to heat. On physical examination there were found 2+ wasting and

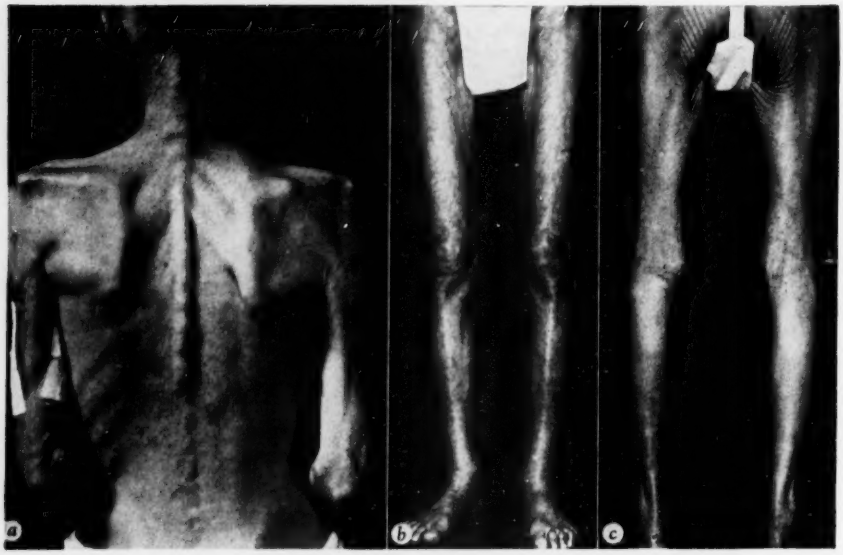

Fig. 4 (Case 27).—Marked wasting of shoulder, arm, and thigh muscles in patient with thyrotoxic myopathy.

Fig. 5 (Case 27).—Muscle biopsy taken from the left biceps muscle. Muscle appears essentially normal. Hematoxylin and eosin; × 105.

weakness of the shoulder girdle muscles, 2 to 3 + wasting and weakness of the pelvic girdle muscles, and slight wasting and weakness of the muscles of the forearms, hands, and legs. The stretch reflexes were normal. There was a static tremor of the outstretched hands; the thyroid gland was diffusely slightly enlarged; there was slight exophthalmos, and the pulse rate was 100 per minute. The blood pressure was 230/90. The basal metabolic rate was + 50%. Roentgenograms of the chest showed no abnormalities. There was no increase in strength following administration of neostigmine, and the results of the curare test were normal. After preparation with administration of strong iodine solution, U. S. P., thyroidectomy was performed on Oct. 26, 1948. In March, 1950, word was received from the patient that she had gained 35 lb. (15.75 kg.) and that her muscles apparently were working well. The high blood pressure persisted.

CASE 31.—A man, aged 35 years, registered at the clinic in March, 1948. He complained of having had nervousness, easy fatigability, and inability to work because of weakness for almost two years. He had lost 47 lb. (21.2 kg.). Physical examination revealed 1 to 2 + wasting and weakness of the shoulder girdle muscles, 2 + wasting and weakness of the pelvic girdle muscles, and slight involvement of the intrinsic muscles of the hands. There were mild exophthalmos and definite diffuse enlargement of the thyroid gland. The pulse rate was 115 and regular. The basal metabolic rate was + 66%. Roentgenograms of the chest showed no abnormalities. There was no increase in strength following the administration of neostigmine; the results of the curare test were normal, and the electromyogram showed no particular evidence of muscle disease. Treatment was started with propylthiouracil. Word was subsequently received that the patient did not regularly take this medication. The follow-up is incomplete.

CASE 32.—A man, aged 58 years, was first seen at the clinic in January, 1948, at which time he complained of loss of weight over a period of two years, intolerance to heat, nervousness, and palpitation. When questioned he commented that he had had so much weakness that he had been able to do only a very small amount of work during the preceding year. He noticed this weakness particularly in the upper arms and shoulder girdle. There had been a loss of 42 lb. (18.9 kg.). On physical examination there were found 1 to 2 + wasting and weakness of the shoulder girdle muscles, 2 + weakness of the pelvic girdle muscles, and slight weakness and wasting of the muscles of the forearms and hands. Stretch reflexes were slightly decreased. There were slight tremor, mild exophthalmos, and mild diffuse enlargement of the thyroid gland, and the pulse rate was 96 per minute. The basal metabolic rate was + 41%, and roentgenograms of the chest showed no abnormalities. There was no increase in strength following the administration of neostigmine; the results of the curare test were normal, and the electromyogram showed no evidence of muscle disease. After preparation with the administration of strong iodine solution, U. S. P., thyroidectomy was performed on Feb. 5, 1948. By late March, 1948, the patient had gained 37 lb. (16.7 kg.) and his strength had returned to normal.

CASE 33.—A man, aged 48 years, registered at the clinic first in 1948. He complained that he was unable to work because his legs were weak and shaky and that from time to time there would be "cramps" in the calves and thighs. These cramps were partially relieved by walking. There had been a loss of 20 lb. (9 kg.) in the preceding two months. Physical examination revealed ± wasting and weakness of the shoulder girdle muscles and 1 to 2 + weakness of the pelvic girdle muscles. Stretch reflexes were normal to mildly hyperactive. There were tremors of the outstretched hands and questionable exophthalmos. There was slight diffuse enlargement of the thyroid gland, and the pulse rate was 80 per minute. The basal metabolic rate was + 55%. Roentgenograms of the chest showed no abnormalities. There was no increase in strength following administration of neostigmine, and the results of the curare test were normal. Following preparation by the administration of strong iodine solution, U. S. P., thyroidectomy was performed on March 22, 1948. Word was received from the patient's local physician in May, 1951, that there was no longer any weakness of the shoulder and pelvic girdle muscles.

CASE 34.—A man, aged 40 years, was first seen at the clinic in February, 1949, at which time he complained of progressive difficulty in walking, particularly in ascending stairs. Associ-

ated with this loss of strength, which had occurred over a period of five months, there had been a loss of 30 lb. (13.5 kg.). There was also tremulousness of the legs, and the patient had noted considerable twitching of the muscles, mainly in the calves. During the month before examination difficulty in holding up the arms had been noted. Physical examination revealed 1 + wasting and weakness of the shoulder girdle muscles and 2 + weakness of the pelvic girdle muscles. There was a great deal of tremulousness and twitching of the muscles of the lower extremities, particularly in the calves. There was slight diffuse enlargement of the thyroid gland, and the pulse rate was 128 per minute. The basal metabolic rate was + 71%, and roentgenograms of the chest showed no abnormalities. There was no increase in strength following the administration of neostigmine; the results of the curare test were normal, and the electromyogram showed no evidence of muscle pathology. (There were no fibrillation potentials present.) After preparation with the administration of strong iodine solution, U. S. P., thyroidectomy was performed on Feb. 25, 1949. The patient was not seen again for a check-up examination, but word was received in September, 1951, that he had returned to full-time work for the first time in two years.

Fig. 6 (Case 35).—Thyroid enlargement; wasting of the deltoids, trapezius muscles, supraspinatus muscles, and other portions of the shoulder girdle in a patient with thyrotoxic myopathy.

Case 35.—A woman, aged 31 years, registered for the first time in February, 1949. She complained of having had loss of weight and severe weakness in the legs over a period of six months. The leg weakness was severe enough to impair the patient's ability to get up and down steps. During the month preceding the examination she had had difficulty in getting her arms into the air in combing her hair. She had lost 27 lb. (12.2 kg.). Physical examination revealed 2 + wasting and weakness of the shoulder girdle muscles (Fig. 6), 2 to 3 + weakness of the pelvic girdle muscles, and slight involvement of the forearms and hands. The stretch reflexes were normal to slightly hyperactive. There was a tendency to generalized tremor, questionable exophthalmos, and mild diffuse enlargement of the thyroid gland. The pulse rate was 96 per minute and regular. The basal metabolic rate was + 59%, and roentgenograms of the chest showed no abnormalities. There was no increase in strength following the administration of neostigmine, and the results of the curare test were normal. After preparation with the administration of strong iodine solution, U. S. P., thyroidectomy was performed on February 25, 1949. Word was received in September, 1949, that the patient's muscle strength and general health had apparently returned to normal.

COMMENT CONCERNING CASES

Case 26, labeled "myositis," is included in detail to draw attention to the similarity of this disorder to "chronic thyrotoxic myopathy." Originally the patient was referred to the sections of neurology from the division of medicine as a question of muscular dystrophy or "thyrotoxic myopathy." The loss of weight, good appetite, nervousness, intolerance to heat, tachycardia, and increased basal metabolic rate

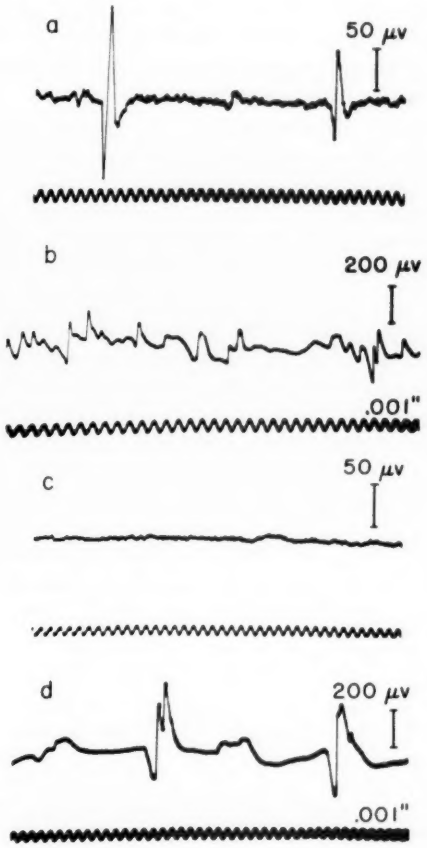

Fig. 7.—(*a* and *b*) Electromyogram of deltoid muscle (Case 26). (*a*) Fibrillation potentials at rest; (*b*) decrease in size of motor unit action potentials. Increased per cent of motor unit action potentials. (*c* and *d*) Electromyogram of essentially normal deltoid muscle (Case 27).

logically indicated the latter diagnosis. Not until determination of protein-bound blood iodine, radioactive iodine studies, and an electromyogram were made did the diagnosis become evident, to be proved by muscle biopsy. Sufficient time has not elapsed to observe the outcome of this case.

In Case 29 the patient was sent to the clinic with a diagnosis of progressive muscular dystrophy. The first two consultants to examine the patient did not actively suspect the presence of hyperthyroidism but referred the problem to the

section of metabolic disease for study because of the loss of weight and tachycardia. There the consultant, who had seen a number of similar patients, made a clinical diagnosis of hyperthyroidism.

Case 33 is purposely included because it is a mild but definite example of "chronic thyrotoxic myopathy." This patient did not have the widespread muscle involvement sometimes present but did have selective weakness of pelvic musculature. The consultant recorded that "on attempting to squat he does well until the buttocks are about 18 in. (45 cm.) from the heels and then he goes down rapidly" and "on attempting to sit down slowly he drops into the chair and cannot arise slowly—he must hunch forward to get up without using his upper extremities." These abnormalities disappeared after treatment.

Case 34 is an example characterized by many muscle twitches. The consultant wrote, "There is a marked tremulousness and also a twitching of the muscles, particularly in the calves. These twitches should not be confused with the fasciculations of amyotrophic lateral sclerosis." This comment was made before the electromyogram was made and is interesting because it indicates that in the clinician's opinion there was a visibly detectable difference between the two abnormalities mentioned.

In Cases 27, 30, and 35 there were severe wasting of muscle substance and a comparatively severe weakness, yet the degree of hyperthyroidism apparent was similar to that in Cases 29, 31, and 34. There appears to be some quantitative dissociation between the degree of muscle involvement and the state of thyroid function. In spite of the great muscle dysfunction, the patients in Cases 27 and 35 recovered completely. Adequate follow-up is not available concerning the patient in Case 30.

GENERAL COMMENT

Table 3 is a collection of some of the clinical data concerning these cases.

Table 4 summarizes a number of facts which may aid in the differential diagnosis of thyrotoxic myopathy, myasthenia gravis, and "myositis," exclusive of evidence concerning the existence of thyrotoxicosis. Chronic thyrotoxic myopathy may be mistaken for "myositis," since patients with the latter often have an elevated basal metabolic rate. If the clinician cannot be certain about the difference, the radioiodine tracer study, determination of protein-bound blood iodine, electromyogram, or muscle biopsy may be needed. A summary of the record of the patient having "myositis" was included to emphasize the similarity between the clinical pictures of the two disorders.

Weakness of the pelvic girdle muscles was present in eight of the nine patients, and these muscles were ordinarily the site of most severe involvement. Some degree of shoulder girdle wasting and weakness was observed in every patient but in seven instances was less severe than that in the pelvic girdle. Wasting and weakness of peripheral muscles was absent or mild in six patients. Eight patients had normal to mildly hyperactive stretch reflexes. This is in contrast to the type of stretch reflex obtained where muscles are involved by "myositis" or progressive muscular dystrophy. Evidence of increased thyroid function is not present in the latter and serves as a basic differential point between it and chronic thyrotoxic myopathy.

TABLE 3.—*Data on Patients Who Had Chronic Thyrotoxic Myopathy**

Case	Age, Yr.	Sex	Shoulder Girdle Wasting and Weakness	Pelvic Girdle Weakness	Additional Muscle Involvement	Stretch Reflexes	Weight Loss, Lb.	Tremor	Exophthalmos	Enlarged Thyroid	Pulse/Min.	B. M. R.	Protein Bound Blood Iodine	Radioiodine Study	X-Ray, Chest	Neostigmine Test	Curare Test	Electromyogram	Treatment	Result
27	55	M	2-3+	2-3+	+	N to +	38	—	1-2	+	96	+32	10.0	+	N	0	N	N	I^{131}	Recovered
28	66	M	1-2+	2+	+	N	45	+	—	—	120	+36	14.7	+	N	N	0	0	I^{131}	Recovered
29	31	M	1-2+	N	N	N to +	36	—	—	±	110	+51	0	0	N	N	N	0	S. I., thyroidectomy	Recovered
30	50	F	2+	2-3+	+	N	40	+	±	±	100	+50	0	0	N	N	N	0	S. I., thyroidectomy	? Muscles OK
31	35	M	1-2+	2+	±	N to +	47	±	±	+	115	+66	0	0	N	N	N	N	Thiouracil	?
32	58	M	1-2+	2+	±	Hypo-N	42	±	+	±	96	+41	0	0	N	N	N	N	S. I., thyroidectomy	Recovered
33	48	M	±	1-2+	N	N to +	20	+	±	±	80	+55	0	0	N	N	N	0	S. I., thyroidectomy	Recovered
34	40	M	1+	2+	N	N	30	+	—	±	128	+71	0	0	N	N	N	0	S. I., thyroidectomy	? Returned to work
35	31	F	2+	2-3+	±	N to +	27	+	±	+	96	+59	0	0	N	N	N	0	S. I., thyroidectomy	Recovered

* 0 = not done, N = normal, — = absent, S. I. = strong iodine solution, U. S. P. (Lugol's solution).

The detection of myasthenia gravis, associated simultaneously with thyrotoxicosis (with or without chronic thyrotoxic myopathy), depends on the use of the neostigmine and curare tests aided by electromyographic study.

It seems likely that chronic thyrotoxic myopathy is a fairly common disorder, although previously considered rare. For three or four decades internists have noted that patients with hyperthyroidism often have weakness of the iliopsoas muscles. This weakness is so commonly present that it is considered a sign of considerable aid in the diagnosis of Graves' disease. This iliopsoas weakness, commonly detected, is a mild form of chronic thyrotoxic myopathy. Case 34 was included because the patient suffered from a relatively mild form of the disorder. That such mild forms do occur has not been emphasized in the literature. The sharp dissociation of the hyperthyroid state and myopathy (mild thyrotoxicosis and very severe myopathy) occurs rarely. Interest in this dissociation may explain the lack of attention directed to the clinical syndrome of moderate to severe hyper-

TABLE 4.—*Differential Points Exclusive of Those Concerning Hyperthyroidism*

	Chronic Thyrotoxic Myopathy	Myasthenia Gravis	"Myositis"
Distribution (commonest)	Pelvic girdle; shoulder girdle	Muscles innervated by cranial nerves	Shoulder girdle; pelvic girdle
Stretch reflexes in involved muscles	Normal to hyperactive	Hypoactive to normal	Hypoactive
Muscle wasting	Present	Rarely present	May be marked in late stages
Neostigmine test	No change	Ordinarily marked improvement	No change
Curare test	Normal	Very sensitive	Normal
Electromyogram	Normal in 3 patients	No activity at rest, decreased size of motor unit potentials, decreasing amplitude of motor unit potentials with continued activity	Fibrilation potentials at rest, decrease in size of motor unit action potentials, increased % polyphasic potentials, increased number of potentials relative to strength of contraction
Biopsy	Normal in 1 patient	Usually normal (lymphorrages)	Mild to marked degeneration of muscle fibers, collections of round cells in interstitial tissue

thyroidism associated with mild to moderate degrees of myopathy. It is altogether likely that the same mechanism is involved in the production of the myopathy, regardless of the degree of thyrotoxicosis present. Though abnormal creatine metabolism in exophthalmic goiter was reported by Shaffer in 1907 [21] and has been studied many times since that day, the position of this abnormality in the pathogenesis of chronic thyrotoxic myopathy is still not understood. Whether the fact that 77% of the patients with chronic thyrotoxic myopathy were men and that 80% of the patients with thyrotoxicosis and myasthenia gravis were women is of significance cannot be stated. That the process accounting for the wasting and weakness of muscle is reversible is indicated by the recovery of all patients having chronic thyrotoxic myopathy who were adequately followed. If it is recognized that this disorder, in some degree, is more frequent than was formerly believed, studies of the metabolism of the abnormal muscle can be more often undertaken.

21. Shaffer, P.: Protein Metabolism in Exophthalmic Goitre, Proceedings of American Society of Biological Chemists, in J. Biol. Chem. **3**:13-14, 1907.

FAMILIAL PERIODIC PARALYSIS

The occurrence of hyperthyroidism and periodic paralysis simultaneously in the same patient is rare. More than 400 cases of familial periodic paralysis are recorded in the medical literature, and in less than 30 of them has there been concurrent hyperthyroidism. In 1931 Dunlap and Kepler [22] reported four cases of this combination of diseases. The complaint of periodic paralysis disappeared when the patients became euthyroid after the thyrotoxicosis was treated. Morrison and Levy [23] described such a case in 1932. The patient was much improved after thyroidectomy but not completely relieved. Hildebrand and Kepler [24] presented an extensive report concerning a fifth case in 1941. Relief was complete following thyroidectomy. Seed [25] in 1947 and Kepner [26] in 1951 described examples of this combination of diseases. In the former instance thiouracil treatment was followed by disappearance of the periodic paralysis, while thyroidectomy in Kepner's case was succeeded by disappearance of the muscle symptoms. In 1934 Biemond and Daniels [27] discovered subnormal quantities of potassium in the serum of a patient having an attack of periodic paralysis (without hyperthyroidism). Since that time many investigators have reported that patients observed by them either do or do not have abnormal quantities of potassium in the serum during attacks. Wolf [28] believes that the attacks of paralysis are a result of acute thyroid deficiency. This view ignores the existence of hyperthyroidism and familial periodic paralysis in the same patient, with the attacks becoming more frequent and severe with increasing intensity of hyperthyroidism and the subsequent disappearance of attacks after thyroidectomy. In two of Kepler's patients complete relief of the two diseases was followed, after a number of years, by recurrence of both the hyperthyroidism and periodic paralysis.

Certain facts from the report of Hildebrand and Kepler's fifth case are of significance. The patient, a man, gave a familial history of periodic paralysis. He had had very mild and infrequent attacks of paralysis, but when hyperthyroidism developed the attacks of paralysis became frequent and severe. The attacks could be precipitated by the intravenous administration of glucose solution, by the injection of insulin, or by both. During the paralysis the serum potassium value was subnormal—the lowest value recorded was 10.0 mg. per 100 cc. In general the lower the serum potassium the more severe the paralysis. The intravenous administration of large doses of potassium salts did not relieve an attack even though the serum potassium concentration was subnormal at the time of the injection.

22. Dunlap, H. F., and Kepler, E. J.: Occurrence of Periodic Paralysis in the Course of Exophthalmic Goiter, Proc. Staff Meet., Mayo Clin. **6**:272-275 (May 6) 1931.

23. Morrison, S., and Levy, M.: The Thyroid Factor in Family Periodic Paralysis: Report of a Case, Arch. Neurol. & Psychiat. **28**:386-393 (Aug.) 1932.

24. Hildebrand, A. G., and Kepler, E. J.: Familial Periodic Paralysis Associated with Exophthalmic Goiter, J. Nerv. & Ment. Dis. **94**:713-721 (Dec.) 1941.

25. Seed, L.: Periodic Paralysis in Patient with Exophthalmic Goiter Controlled by 6-Prophylthiouracil, West. J. Surg. **55**:640-646 (Dec.) 1947.

26. Kepner, R. D.: Periodic Paralysis Associated with Hyperthyroidism: A Case Report, J. Neuropath. & Clin. Neurol. **1**:316-319 (Oct.) 1951.

27. Biemond, A., and Daniels, A. P.: Familial Periodic Paralysis and Its Transition into Spinal Muscular Atrophy, Brain **57**:91-108 (June) 1934.

28. Wolf, A.: The Effective Use of Thyroid in Periodic Paralysis, New York J. Med. **43**:1951-1963 (Oct. 15) 1943.

A sixth case can now be added to the group previously reported, although complete laboratory studies are not available.

A man, aged 49 years, registered in November, 1940, at which time he complained of falling spells. During these episodes his legs would become so weak that he would sink to the ground. He would be unable to get up for several minutes. Gradually the strength would return to normal. The attacks occurred as often as four times in one day and as seldom as one time per week. Emotion had no effect in precipitating the episodes or in prolonging them. The patient related that for a number of years his father had had a similar trouble. The father would develop weakness of his legs, which on many occasions progressed to complete paralysis lasting for an hour or more. There was never any pain associated with the complaints in either person. There had been increasing loss of weight, perspiration, nervousness, and irritability. Owing to enlargement of the thyroid gland the patient's collar size had changed from 16 to 17 during the month before admission. He had lost 20 lb. (9 kg.). Physical examination revealed unequal palpebral fissures, lid lag on the right, and a fine tremor of the hands. The pulse rate was 80 per minute and regular, and the blood pressure was 115/75. The basal metabolic rate was + 23%. The patient did not feel that he could spend the time needed for special laboratory studies. Thyroidectomy was performed, and the postoperative course was uneventful. Word was received from the patient three months later that he was not having the episodes of paralysis of the legs.

COMMENT

The faulty mechanism present in the muscle of people with periodic paralysis is not well understood. It is generally agreed that the concentration of potassium in the serum has something to do with muscle power. Gammon and associates,[29] Watson,[30] Seed,[25] and others have reported cases in which the blood serum potassium remained within normal limits during the attack. Gass, Cherkasky, and Savitsky [31] very carefully studied a patient with periodic paralysis. They induced attacks by giving glucose—then potassium balance studies were done. They found no increased excretion of potassium in the urine or stool but did record a decrease in the serum potassium coincident with the development of paralysis. There was no change in the potassium concentration of the red blood cells. This would simply indicate a shift in the position of certain quantities of potassium from the serum to other areas, and apparently not into red blood cells. Potassium may become concentrated in muscle at such times, but this has not been finally established. Where the potassium went or how it worked the authors could not say. Hildebrand and Kepler [24] and Ziegler [32] have administered potassium intravenously to patients having paralysis concomitantly with low serum potassium levels; however, in neither instance was there any immediate improvement of the paralysis. This would indicate that some other mechanism is at work or that a change takes place at such a low rate of speed that no effect is detected following the injection. In other disorders it is sometimes difficult to correlate quantitatively the serum potassium level and the muscle strength present. We have seen patients, receiving corticotropin for myasthenia gravis, who had marked increase in weakness coincident

29. Gammon, G. D.; Austin, J. H.; Blithe, M. D., and Reid, C. G.: The Relation of Potassium to Periodic Family Paralysis, Am. J. M. Sc. **197**:326-332 (March) 1939.

30. Watson, C. W.: Familial Periodic Paralysis: Report of a Case Showing No Changes in Serum Potassium Level with a Description of Electroencephalographic Findings, Yale J. Biol. & Med. **19**:127-135 (Oct.) 1946.

31. Gass, H.; Cherkasky, M., and Savitsky, N.: Potassium and Periodic Paralysis: A Metabolic Study and Physiological Considerations, Medicine **27**:105-137 (Feb.) 1948.

32. Ziegler, D. K.: Familial Periodic Paralysis: Report on 2 Families, with Observations on the Pathogenesis of the Syndrome, Arch. Int. Med. **84**:419-430 (Sept.) 1949.

with an abnormally low serum potassium. Some of these patients markedly improved following elevation of the serum potassium, while others had their strength unchanged. That there is more to this matter than the simple concentration of potassium in the serum is obvious.

The relationship of disordered thyroid function to periodic paralysis has been little studied. In the recorded cases there was definite improvement or complete relief of the periodic paralysis after effective treatment of the hyperthyroidism. At the present time both clinical and laboratory evidence indicates that the two are separate diseases. However, clinical data make us believe that periodic paralysis may exist, in some instances, as a latent abnormality which becomes a manifest abnormality as thyrotoxicosis develops. The manner in which this temporary change is produced is not apparent. It is obvious that the treatment is control of the hyperthyroidism. It seems just as likely that euthyroid individuals with periodic paralysis will not have the latter affected by being made myxedematous. The association of hyperthyroidism and periodic paralysis is much more frequent than would be expected to occur by chance. The significance of this relationship is not known.

EXOPHTHALMIC OPHTHALMOPLEGIA

The term "exophthalmic ophthalmoplegia" has been widely used since Brain [33] chose it for the title of a paper. He believed it a syndrome distinct from myasthenia gravis and thyrotoxicosis. In contrast, Mulvany [34] questions the existence of the clinical entity of exophthalmic ophthalmoplegia but believes that such cases belong either to a "thyrotoxic" or to a "thyrotropic" group. Apparently this difference of opinion concerns classification and concepts of pathogenesis, since the simultaneous existence of exophthalmos and extraocular muscle paresis or paralysis is a well-known combination of physical signs. In this brief discussion the term "exophthalmic ophthalmoplegia" refers only to the simultaneous occurrence of the two physical abnormalities and does not imply any particular concept concerning pathogenesis.

Table 5 presents in simplified form some observations concerning 21 patients with exophthalmic ophthalmoplegia. Measurement of exophthalmos was done with Hertel's exophthalmometer, and the result is recorded in millimeters. The measurement is the anteroposterior distance from the external margin of the orbit to the apex of the cornea. (It is well known that the accurate measurement of exophthalmos is difficult and that measurement of the exophthalmos of an eye may vary when done by different examiners.)

The Table shows that there were 17 women and 4 men and that the age range was from 28 to 61 years. The degree of ophthalmoplegia paralleled that of the exophthalmos in most cases. However, in Cases 38, 43, and 55 there was proportionately more ophthalmoplegia than exophthalmos. The superior rectus muscles were most frequently and most severely involved. Five patients had moderate to severe degrees of hyperthyroidism at the time the exophthalmic ophthalmoplegia

33. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, with Pathological Report on Ocular Muscles and Thyroid Glands, Quart. J. Med. **7**:293-323 (April) 1938.

34. Mulvany, J. H.: The Exophthalmos of Hyperthyroidism: A Differentiation in the Mechanism, Pathology, Symptomatology, and Treatment of 2 Varieties, Am. J. Ophth. **27**:589-612 (June); 693-712 (July); 820-832 (Aug.) 1944.

TABLE 5.—*Data on Patients Who Had Exophthalmic Ophthalmoplegia*

Case	Sex	Age, Yr.	Exophthalmo., Mm.		Ophthalmoplegia*		Thyroid Enlargement	Pulse/Min.	B. P.	B. M. R.	Treatment†	After Thyroidectomy	Time, Mo.	Result Follow-Up
			OD	OS	OD	OS						Exophthalmos		
36	F	53	23	25	3	3	—	76	120/80	−12	S. I., thyroid	+	0	0
37	F	60	23.5	24	3	3	±	109	200/100	+37	S. I.	..	12	OD, 19.0; OS, 19.0; euthyroid
38	F	45	21	20	2	2	—	88	134/84	+2	None	±	30	Exophthalmos same; ophthalmoplegia almost gone
39	M	42	25.5	24.5	3	3	—	77	132/78	+11	S. I., thyroid	+	0	0
40	F	48	21	21	1	1	—	79	124/86	+4	S. I.	Never hyperthyroid	0	0
41	F	28	23	21	3	±	+	90	115/65	+24	S. I., thyroidectomy	..	60	Euthyroid; exophthalmos same
42	F	46	19	19	1-2	1-2	+	100	110/70	+17	S. I., x-ray to orbits	..	10	Euthyroid; exophthalmos same; chemosis gone
43	F	56	15	20	N	2-3	+	100	130/70	+37	S. I., thyroidectomy	..	12	Euthyroid;
44	M	61	29	27	4	3	—	84	115/80	−4	S. I.	..	60	eyes unchanged
45	F	49	19	14	1-2	N	±	76	110/75	−6	S. I.	+	48	Unchanged
46	F	45	22	22	3	3	—	100	122/78	−10	S. I.	Never hyperthyroid	0	0
47	F	29	22	20	3	3	—	100	130/94	+3	S. I., thyroid	+	0	0
48	F	59	29	26	1-2	1-2	—	96	180/80	−2	S. I., thyroid	+	0	0
49	F	47	23	29	2-3	2-3	—	84	200/110	+4	S. I., x-ray to orbits	Never hyperthyroid	36	Unchanged
50	M	41	16	21	1	2	+	88	135/90	+27	S. I., thyroid	..	18	Euthyroid; eyes unchanged
51	F	34	18	22	0-1	2	—	88	134/80	+7	S. I., thyroid	+	72	Euthyroid; exophthalmos worse
52	F	33	22	22	2	2	±	99	120/70	+40	S. I., x-ray, thyroidectomy 2X	+	6	Eyes much worse; euthyroid
53	M	41	24	25	3-4	3-4	+	88	160/80	+51	S. I., thyroidectomy	..	0	0
54	F	48	19	15	2	N	—	64	120/70	+7	S. I., thyroidectomy	..	18	Euthyroid; eyes worse
55	F	40	18.5	18	2	2	+	120	140/70	+40	S. I., thyroidectomy	Never hyperthyroid	..	.....
56	F	46	21	22	1-2	1-2	+	80	178/110	+1	S. I.	..	36	Euthyroid (post-op. S. I.); exophthalmos worse
												Never hyperthyroid	0	.....

* Grades of ophthalmoplegia are as follows: 1 = impairment of upward rotation; 2 = paralysis of upward rotation with some other muscle weakness; 3 = paralysis of upward rotation with severe involvement of other muscles; 4 = loss of all voluntary power of ocular rotation.

† S. I. = strong iodine solution, U. S. P.

developed. Seven patients developed this syndrome after thyroidectomy and while euthyroid. In five patients there was no evidence of previous thyrotoxicosis, and the consultant found no signs of it at the time of the examination. Protein-bound blood iodine determinations and radioiodine tracer studies were not done. Patient 47 had myasthenia gravis, as determined by her reaction to the administration of neostigmine and to the curare test. Neostigmine and curare tests in two other patients failed to reveal evidence of the presence of myasthenia gravis. Treatment consisted of the administration of strong iodine solution, U. S. P., followed by thyroidectomy and strong iodine solution, U. S. P., or strong iodine solution, U. S. P., and thyroid after the operation. When there was no hyperthyroidism or very mild hyperthyroidism, strong iodine solution, U. S. P., or strong iodine solution, U. S. P., and thyroid were prescribed. So far as the ophthalmoplegia is concerned, the results of treatment were poor in most instances.

COMMENT

Exophthalmic ophthalmoplegia ordinarily occurs in both eyes but may be unequal in quantity. Drescher and Benedict [35] have demonstrated that the less prominent of the two eyes is also usually involved in the exophthalmos of exophthalmic goiter. They found that asymmetry of the two eyes in excess of 7 mm. was uncommon in exophthalmic goiter.

Ophthalmoplegia of recognizable degree exists rather infrequently in patients with Graves' disease. The degrees of exophthalmos and ophthalmoplegia commonly parallel one another; however, severe exophthalmos can occur without demonstrable ophthalmoplegia and extreme degrees of ophthalmoplegia may be present when there is only mild exophthalmos. The elevators of the globe are the most frequently involved extraocular muscles, but the occurrence of severe ophthalmoplegia with very mild exophthalmos indicates that simple stretching of the muscles is not the full explanation for the ophthalmoplegia. One eye may be more impaired in its movements than the other, and the ophthalmoplegia, when it is part of the picture of Graves' disease, is usually accompanied by edema of the lids, chemosis, and photophobia. These characteristics usually make easy the recognition of the ophthalmoplegia of Graves' disease in a majority of cases, even though it is true that these ocular changes may occur in a person who shows none of the other signs of thyrotoxicosis and in whom all laboratory studies may confirm the presence of a euthyroid state. In the ophthalmoplegia associated with myasthenia gravis there is ordinarily no chemosis, swelling of the lids, or edema of the conjunctiva and there is generally marked asymmetry in the degree of involvement of congruous muscles in the two eyes.

The mechanism and pathogenesis of the ophthalmoplegia have not been fully explained. Ophthalmoplegia is common in myasthenia gravis, and it sometimes does not respond as well to neostigmine or as adversely to curare as does the function of other involved muscles in the same patient. Some authors [36] have

35. Drescher, E. P., and Benedict, W. L.: Asymmetric Exophthalmos, Arch. Ophth. **44**:109-128 (July) 1950.

36. Wedd, A. M., and Permar, H. H.: Ophthalmoplegia in Graves' Disease, Am. J. M. Sc. **175**:733-740 (June) 1928. Naffziger, H. C., and Jones, O. W., Jr.: The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99**:642-683 (Aug. 20) 1932. Cohen and King.[6]

suggested that the changes in the extraocular muscles in exophthalmic ophthalmoplegia are similar to those seen in myasthenia gravis. That some patients with exophthalmic ophthalmoplegia do not have myasthenia gravis has been demonstrated in several instances in this study by the neostigmine and curare tests. The observation that neostigmine in some cases materially improves the extraocular muscle weakness has not been confirmed by us.

Naffziger,[37] Dobyns,[38] and others have studied the orbital contents in exophthalmic ophthalmoplegia. Enlarged extraocular muscles, with edema, infiltration with lymphocytes and connective tissue, and marked increase in the fat in the muscles were found. Rundle and Pochin [39] have demonstrated a disproportionate increase in the fat content of various extraocular muscles. Although not enough cases were studied to allow them to ascribe the disproportionate muscle weakness to the differentially increased fat content, they believed there might prove to be some relationship. It is possible that these organic changes may alter end plate structures, leading to faulty neuromuscular transmission. This does not imply that such faulty transmission need be the same as or similar to that existing in myasthenia gravis. Unfortunately, electromyographic studies using microelectrodes to determine the state of end plate potentials are not available for consideration in studying the mechanisms involved in the muscle paresis.

Exophthalmic ophthalmoplegia may be associated with thyrotoxicosis of any degree of severity; may develop after the patients have become euthyroid and, rarely, after they have become myxedematous, and may occur in persons who have never had clinical thyrotoxicosis. This variation in the sequence of events has led to the conclusion that the thyroid is not the apparent source of a substance which initiates the production of exophthalmic ophthalmoplegia. This variation in the sequence of events has also stimulated the search for another substance which may be capable of producing exophthalmic ophthalmoplegia in the presence or absence of normal or abnormal thyroid secretion. Smelser,[40] Paulson,[41] Aird,[42] and pochin [43] have produced exophthalmos in animals by the administration of extracts of the anterior lobe of the pituitary. That inferences drawn from such work, conducted on animals, may not apply fully to the human is obvious. Rawson and

37. Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, with Special Reference to Alterations in the Extra-Ocular Muscles and the Optic Disks, Arch. Ophth. **9**:1-11 (Jan.) 1933.

38. Dobyns, B. M.: Exophthalmos and Tissue Changes in the Guinea Pig Following Administration of the Thyroid Stimulating Hormone of the Pituitary Gland, West. J. Surg. **54**:411-425 (Nov.) 1946.

39. Rundle, F. F., and Pochin, E. E.: The Orbital Tissue in Thyrotoxicosis: A Quantitative Analysis Relating to Exophthalmos, Clin. Sc. **5**:51-74 (Aug.) 1944.

40. Smelser, G. K.: Experimental Production of Exophthalmos Resembling That Found in Graves' Disease, Proc. Soc. Exper. Biol. & Med. **35**:128-130 (Oct.) 1936.

41. Paulson, D. L.: Experimental Exophthalmos in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **36**:604-605 (June) 1937.

42. Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Extract, Arch. Ophth. **24**:1167-1174 (Dec.) 1940.

43. Pochin, E. E.: Exophthalmos in Guinea Pigs Injected with Pituitary Extracts, Clin. Sc. **5**:75-91 (Aug.) 1944.

associates [44] have demonstrated that tissue slices taken from thyroids of patients with Graves' disease inactivated about twice as much thyroid-stimulating hormone as equal amounts of normal human thyroid tissue. Whether the basic pathologic process begins in the thyroid or in the pituitary has not been established. However, the fact remains that a fraction of thyroid-stimulating hormone capable of producing this phenomenon in the human has not been demonstrated. Whether such a fraction exists, whether the interaction of two or more components is required, or whether some thus far unsuspected mechanism is present remains to be discovered.

Treatment of exophthalmic ophthalmoplegia with iodine, thyroid, corticotropin, cortisone, and roentgen radiation to the pituitary or orbits or both, or combinations of these agents, has not been followed by consistently favorable response, although in isolated instances regression of symptoms has been noted after each of these procedures. The associated chemosis, swelling of the lids, edema of the conjunctiva, and photophobia apparently are more often benefited than are the basic exophthalmosis and ophthalmoplegia. This failure of a consistent response to varied methods of treatment implies the presence of some degree of irreversibility in the pathologic process, the presence of multiple mechanisms in pathogenesis, or the existence of a totally unsuspected cause.

HYPOTHYROIDISM

It has long been recognized that impaired memory, mental retardation, sluggishness, and generalized slowing of muscle action are a prominent part of the clinical picture of hypothyroidism. Himwich and associates [45] demonstrated an increase in cerebral oxygen consumption in cretins following the administration of thyroid. (Using a different technic Sokoloff and associates [46] did not find the converse to be true in hyperthyroidism.) Ross and Schwab [47] reported that there was an absence of the alpha waves and a decrease in the amplitude of the other brain waves in the electroencephalograms of patients with myxedema. However, the mechanism involved in the decreased speed of muscle function has been little studied. Thorn [48] observed that small doses of thyroid will produce creatinuria in myxedematous patients, while this was not true in normal subjects. The significance of this observation is not known. For more than 30 years the decreased speed of the biceps and Achilles tendon stretch reflexes in myxedema has proved useful at the Mayo Clinic in the diagnosis of this disorder (Fig. 8). Such a clinical

44. Rawson, R. W.; Graham, R. M., and Riddell, C. B.: Physiological Reactions of the Thyroid Stimulating Hormone of the Pituitary: II. The Effect of Normal and Pathological Human Thyroid Tissues on the Activity of the Thyroid Stimulating Hormone, Ann.. Int. Med. **19**:405-414 (Sept.) 1943.

45. Himwich, H. E.; Daly, C.; Fazekas, J. F., and Herrlich, H. C.: Effect of Thyroid Medication on Brain Metabolism of Cretins, Am. J. Psychiat. **98**:489-493 (Jan.) 1942.

46. Sokoloff, L.; Wechsler, R. L.; Balls, K., and Kety, S.: The Relation of the Cerebral O_2 Consumption to the Total Body Metabolism in Hyperthyroidism, abstracted, J. Clin. Invest. **29**:847 (June) 1950.

47. Ross, D. A., and Schwab, R. S.: The Cortical Alpha Rhythm in Thyroid Disorders, Endocrinology **25**:75-79 (July) 1939.

48. Thorn, G. W.: Creatine Studies in Thyroid Disorders, Endocrinology **20**:628-634 (Sept.) 1936.

observation in itself indicates the probable existence of pathologic physiology in nerve or muscle function or both. Certain changes in muscle shape and texture have also been noted.

The following cases are presented to draw further attention to these observations and the significance of them.

CASE 57.—A woman, aged 25 years, was first seen in July, 1946, at the clinic, at which time she complained of cramps in the legs and nervousness of eighth months' duration. Thyroidectomy had been performed in April, 1945. The consultant in the division of medicine observed one of the cramps and noted that it "consisted of a localized muscle contraction, 3 to 4 inches in diameter, very hard and apparently painful, lasting about a minute." Examination did not reveal the presence of any form of tetany. The consultant in the section of neurology recorded that "the muscles seem hypertrophied, excessively hard to palpation and the reflexes are of definite myxedema type." The pulse rate was 76 per minute and the blood pressure 112/70. The basal

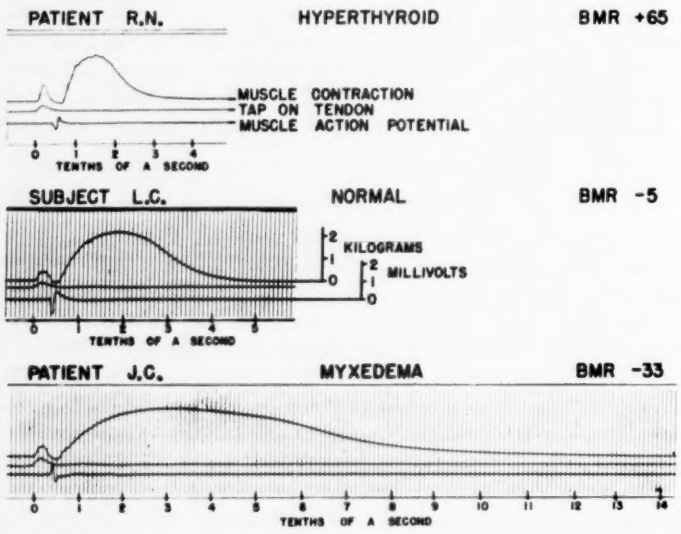

Fig. 8.—Examples of the ankle jerk in hyperthyroid, normal, and myxedematous persons. The contraction and relaxation phases of the response of the muscles are both prolonged in myxedema. In comparison with the normal response, however, the relaxation time is increased relatively more than the contraction time. In addition, the first half of the relaxation phase is often prolonged more than the last half. The appearance of an "angle" or shoulder in the relaxation phase is not uncommon. (From Lambert, E. H.; Underdahl, L. O.; Beckett, S., and Mederos, L. O.: A Study of the Ankle Jerk in Myxedema, *J. Clin. Endocrinol.* **11**:1186-1205 (Oct.) 1951; reproduced with permission of the publisher, Charles C Thomas.)

metabolic rate was —20%, blood calcium 9.8 mg. per 100 cc., phosphorus 3.1 mg. per 100 cc., cholesterol 246 mg. per 100 cc., and the urinary excretion of 17 ketosteroids 5.7 mg. in 24 hours. No creatine was demonstrated in a 24-hour specimen of urine. Graphic studies by Dr. Lambert demonstrated significant reduction in the speed of contraction and relaxation of the muscle in the Achilles tendon reflex. A diagnosis of myxedema was made, and thyroid was administered. Four weeks later the basal metabolic rate was +1%, and the blood cholesterol was 150 mg. per 100 cc. The patient was seen again one year later, at which time she stated that the muscle cramps had disappeared. Examination showed that the calf muscles no longer seemed hypertrophied and excessively hard and the Achilles tendon reflex was normally active. The basal metabolic rate was —1% and the blood cholesterol 143 mg. per 100 cc.

CASE 58.—A man, aged 36 years, registered in October, 1947. He complained of having had increasing weakness for the preceding four years. A diagnosis of Addison's disease had been made elsewhere. Physical examination disclosed the following abnormalities: dry yellowish skin, slow speech, general thickening of subcutaneous tissues, and a very "slow return of the ankle jerks." The pulse rate was 78 per minute and the blood pressure 100/78. A clinical diagnosis of myxedema was made. Routine laboratory tests and a roentgenogram of the chest were normal. The basal metabolic rate was —29%, the blood cholesterol 327 mg. per 100 cc., and the excretion of urinary 17-ketosteroids 4.2 mg. in 24 hours. Graphic examination by Dr. Lambert demonstrated the presence of an abnormality similar to that detailed in Case 57. Thyroid was administered. Three months later the basal metabolic rate was —6% and the blood cholesterol 240 mg. per 100 cc. At that time the patient had no complaints and the Achilles reflex was normal. He was last seen at the clinic in August, 1948. There were no complaints.

CASE 59.—A woman, aged 34 years, first registered in February, 1948, at which time she complained of swellings all over her body. In 1944 a diagnosis of hyperthyroidism had been made and she had been treated with strong iodine solution, U. S. P. Three months later she began to notice swelling of the legs, arms, hands, and face. In September, 1947, there was thick speech and marked fatigue of the upper extremities and jaws during meals. A tentative diagnosis of "myositis" was made elsewhere. Physical examination revealed thick speech, large tongue, and "very slow relaxation of the Achilles tendon reflex." The neurologic consultant noted, "The muscles are firm and seem somewhat fibrous. There is marked slowness of movement, especially in speech and finger action. Strength is probably normal." The pulse rate was 68 per minute and the blood pressure 106/86. The administration of neostigmine methylsulfate was not followed by change in strength. Routine laboratory studies and roentgenograms of the chest and head showed no abnormalities. The basal metabolic rate was —20%. The blood cholesterol was 397 mg. per 100 cc., blood calcium 10.0 mg. per 100 cc., and blood phosphorus 4.2 mg. per 100 cc. The electromyogram combined with special graphic studies disclosed significant reduction in the speed of contraction and relaxation of the muscle in the Achilles tendon reflex. A diagnosis of myxedema, possibly as a result of thyroiditis, was made. Thyroid was prescribed. One month later the basal metabolic rate was —7%, and the blood cholesterol was 257 mg. per 100 cc. The patient's complaints were much improved, and it was noted by the consultant that the muscles were "much softer" and the reflexes were "already more lively."

COMMENT

As has been noted, the abnormal stretch reflexes and unusual "feel" of the muscles have aided the clinician in the diagnosis of myxedema for three decades. Dr. Henry Woltman was, to our knowledge, the first to make this observation and following his suggestion Chaney [49] in 1924 made graphic records which demonstrated the "delayed reaction" of the stretch reflexes in myxedema. Others [50] have confirmed his observations. Little was done to determine the accuracy of the observation as a diagnostic aid or to investigate the site and mechanism of the abnormality until 1951, when Lambert and his associates [51] reported "A Study of the Ankle Jerk in Myxedema." These authors devised a technique for accurately measuring the speed of contraction and relaxation of the muscle in the stretch reflex, and by including simultaneous electromyographic and muscle temperature

49. Chaney, W. C.: Tendon Reflexes in Myxedema: A Valuable Aid in Diagnosis, J. A. M. A. **82**:2013-2016 (June 21) 1924.

50. Armstrong, C. D.: Case of Myxedema With Ascites, Anemia, Myxedema Heart, Angina and Delayed Relaxation of Reflexes, with Note on Therapeutic Effects of Testosterone Proprionate, Stanford M. Bull. **2**:25-36 (Feb.) 1944. Harrell, G. T., and Daniel, D.: Delayed Relaxation of Tendon Reflexes as an Aid in the Diagnosis of Myxedema, North Carolina M. J. **2**:549-551 (Oct.) 1941.

51. Lambert, E. H.; Underdahl, L. O.; Beckett, S., and Mederos, L. O.: A Study of the Ankle Jerk in Myxedema, J. Clin. Endocrinol. **11**:1186-1205 (Oct.) 1951.

recordings they were able to demonstrate that the slow response of the stretch reflex in myxedema is not due to "abnormal activity of the neural elements of the reflex or of the mechanism of excitation of the muscle" or to a lowered temperature of the muscle but is the result of an "abnormality of the contractile mechanism of the muscle." They further demonstrated that the stretch reflex in myxedema is not the same as that observed in myotonia. Seventy-seven per cent of the patients with myxedema studied by them had stretch reflexes slowed beyond the range for euthyroid responses and "the speed of response increased parallel with the increase in basal metabolic rate in 55 patients with myxedema who were treated with desiccated thyroid." The authors also observed that patients having subnormal basal metabolic rates associated with diseases other than myxedema had stretch reflex responses within normal limits.

It is apparent that there is some alteration in muscle metabolism which changes the speed of the intramuscular processes which bring about shortening and lengthening of the muscle fibers. That this abnormal process is associated with subnormal quantities of available thyroid hormone has been demonstrated clinically and confirmed in the laboratory. The mechanism of this action of thyroid hormone on muscle metabolism is not understood. However, the recognition of this physical sign may be of considerable aid in the diagnosis of obscure cases of myxedema.

SUMMARY

Clinical experience and pharmacologic evidence indicate that myasthenia gravis and hyperthyroidism, as they are known today, are separate diseases. The administration of neostigmine does not change the weakness of hyperthyroidism but does greatly alter the weakness of myasthenia gravis. Patients with hyperthyroidism show a normal response to the injection of *d*-tubocurarine, whereas patients with myasthenia gravis are highly sensitive to this drug. There is no consistent relationship between the course of the two diseases. When the two diseases occur together, treatment is a serious problem. The use of I^{131} may be of great aid in therapy of the hyperthyroidism, since thyroidectomy often cannot be performed safely.

Chronic thyrotoxic myopathy is a fairly common disorder although previously considered rare. Most frequently the weakness associated with this disorder is in the pelvic girdle although the shoulder girdle and peripheral muscles may be involved. The stretch reflexes are ordinarily normal. The weak muscles are not strengthened by the administration of neostigmine and are not unusually sensitive to curare. Mild thyrotoxicosis associated with severe myopathy is rare.

The coincident occurrence of periodic paralysis and hyperthyroidism is rare, although the association of the two conditions is much more frequent than would be expected to occur by chance. In the recorded cases there has been definite improvement or complete relief of the periodic paralysis after effective treatment of the hyperthyroidism. Clinical and laboratory evidence indicates that the two are separate diseases. Periodic paralysis may exist, in some instances, as a latent abnormality which becomes manifest as hyperthyroidism develops.

The mechanism and pathogenesis of exophthalmic ophthalmoplegia have not been fully explained. The ophthalmoplegia is not produced by a mechanism similar to that which produces ophthalmoplegia in myasthenia gravis. The exophthalmos is most likely a result of enlargement of the contents of the orbit, in which edema,

infiltration with lymphocytes, and a marked increase of the fat in the extraocular muscles and other orbital tissues all play a part. The ophthalmoplegia is apparently a result of the intrinsic changes in the extraocular muscles. The pathogenesis of these changes in the human is not known.

Hypothyroidism produces a fundamental abnormality in the contractile mechanism of muscle. This abnormality is not observed in other diseases which lower the basal metabolic rate and is not the same as myotonia.

Thyroid dysfunction has been shown to be intimately associated with muscle function. In the group of cases studied this effect appears to be primarily upon intrinsic muscle metabolism rather than upon the nervous system with secondary effects upon muscle action.

EPIDEMIOLOGY OF PENICILLIN- AND AUREOMYCIN-RESISTANT STAPHYLOCOCCI IN A HOSPITAL POPULATION

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DURING the past several years it has become apparent that there are an increasing number of staphylococci which are resistant to the concentrations of penicillin usually obtained in patients.[1] It also seemed likely that a similar change was taking place with respect to the sensitiveness of staphylococci to the action of aureomycin, oxytetracycline (Terramycin), and chloramphenicol.[2]

The increased resistance of these organisms observed among patients may occur by either or both of the following mechanics: 1. Strains sensitive to the antibiotic and carried by a patient at the time the antibiotic is administered may become more resistant because of exposure to the drug. 2. Strains which are resistant to the antibiotic at the time of its introduction or those which subsequently become resistant may spread to other persons (including some who are not receiving antibiotic therapy).

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1. (*a*) Barber, M.: Coagulase-Positive Staphylococci Resistant to Penicillin, J. Path. & Bact. **59**:373-384, 1947. (*b*) Finland, M., and Haight, T. H.: Antibiotic Resistance of Pathogenic Staphylococci: Study of 500 Strains Isolated at Boston City Hospital from October, 1951 to February, 1952, A. M. A. Arch. Int. Med. **91**:143-158, 1953. (*c*) Koch, M. L., and Bourgeois, R. W.: Report on Further Increase in the Incidence of Drug-Resistant Pathogenic Staphylococci Encountered in the Hospital Laboratory, Antibiotics & Chemother. **2**:229-233, 1952. (*d*) Jackson, G. G.; Vicher, E. R., and Soska, J. W.: Clinical Observation of Changes in Sensitivity of Bacteria to Antibiotics, Am. J. Clin. Path. **23**:297-302, 1953. (*e*) Martin, T. D. M., and Whitehead, J. E. M.: Carriage of Penicillin-Resistant Staph. Pyogenes in Healthy Adults, Brit. M. J. **1**:173-175, 1949. (*f*) Martyn, G.: Staphylococci in the Newborn: Their Coagulase Production and Resistance to Penicillin and Streptomycin, ibid. **1**:710-712, 1949. (*g*) Needham, G. M., and Nichols, D. R.: Recent Changes in Sensitivity of Micrococci Pyogenes to Various Antibiotic Agents, J. Lab. & Clin. Med. **41**:150-156, 1953. (*h*) Spink, W. W.: Clinical and Biologic Significance of Penicillin-Resistant Staphylococci Including Observations with Streptomycin, Aureomycin, Chloramphenicol and Terramycin, ibid. **37**:278-293, 1951. (*i*) Summers, G. A. C.: Penicillin-Resistant Staphylococci: Distribution Among Outpatients, Lancet **1**:135-137, 1952. (*j*) Thompson, B. A., and Schwabacher, H.: The Incidence of Penicillin-Resistant Staphylococci in a Semi-Closed Community, J. Clin. Path. **4**:350-354, 1951.

2. Cairns, H. J. F., and Summers, G. A. C.: Penicillin-Resistant Staphylococci: Incidence in Relation to Length of Stay in Hospital, Lancet **1**:446, 1950. Footnote 1*b*, *c*, and *g*.

Several studies [3] have shown that hospital personnel are important in the spread of antibiotic-resistant bacteria. The proportion of infections caused by resistant organisms is higher when such infections are acquired in the hospital than among those acquired in the community at large.

In this paper we shall consider some of the factors which we have found to be related to the spread of resistant staphylococci within a hospital population.

MATERIAL AND METHODS

Clinical material for the study was obtained from the wards of the Municipal Contagious Disease Hospital of Chicago. During the period of observation the average daily patient census was 100 and the number of personnel in relatively close contact with the patients averaged 80. Each patient was individually isolated or isolated as a member of a group of patients having the same disease. The material reported was derived from cultures obtained during the nine-month period of July, 1951, to April, 1952. Depending on the admission rate, a throat culture was obtained from alternate patients or from every third or every fourth patient, and in about half the cases a nose culture was taken also at the time the patient was admitted to the hospital [4] and once a week until discharge. Some of these patients were selected at random for further study, and cultures were done in the home every two weeks for another six weeks or longer. The results of the latter study have been published elsewhere.[5] During the early months of the study only throat cultures were done; however, during the last four months of the study both nose and throat cultures were done. Thus, among 357 patients cultures of the throats only of 181 were made and cultures were made from both the nares and throats of 176. Nose and throat cultures were made of a portion of the personnel involved in patient care in December, 1951, and again, at the end of the study, in April, 1952.

Three groups of patients were observed during the entire study; the first received no antibiotics; the second, penicillin, and the third, aureomycin.[6] In addition, during the last five months of the study, a group of patients receiving both aureomycin and penicillin was added.[7] Almost all the patients who received penicillin were given an aqueous penicillin procaine suspension intramuscularly, 300,000 units daily for 5 to 10 days. The dose of aureomycin generally used was 25 to 50 mg. per kilogram every 24 hours, orally. For a few patients in each group larger doses of the antibiotics were used.

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3. Barber, M.: Staphylococcal Infection Due to Penicillin-Resistant Strains, Brit. M. J. **2**:863-865, 1947. Barber, M.; Hayhoe, F. G. J., and Whitehead, J. E. M.: Penicillin-Resistant Staphylococcal Infection in a Maternity Hospital, Lancet **2**:1120-1125, 1949. Beigelman, P. M., and Rantz, L. A.: The Clinical Importance of Coagulase-Positive, Penicillin-Resistant Staphylococcus Aureus, New England J. Med. **242**:353-358, 1950. Clarke, S. K. R.; Dalgleish, P. G., and Gillespie, W. A.: Hospital Cross Infections with Staphylococci Resistant to Several Antibiotics, Lancet **1**:1132-1135, 1952. North, E. A., and Christie, R.: Observations on the Sensitivity of Staphylococci to Penicillin, M. J. Australia **2**:44-46, 1945. Reiss, E.; Pulaski, E. J.; Amspacher, W. H., and Contreras, A. A.: Penicillin Sensitivity of Staphylococci, New England J. Med. **246**:611-612, 1952. Rountree, P. M., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, Lancet **2**:501-504, 1949. Rountree, P. M., and Barbour, R. G. H.: Nasal Carrier Rates of Staphylococcus Pyogenes in Hospital Nurses, J. Path. & Bact. **63**:313-325, 1951. Rountree, P. M.; Barbour, R. G. H., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, Lancet **1**:435-436, 1951.

4. These will be referred to as "admission cultures."

5. Dowling, H. F.; Lepper, M. H., and Jackson, G. G.: Observations on the Epidemiological Spread of Antibiotic-Resistant Staphylococci, with Measurement of Change in Sensitivity to Penicillin and Aureomycin, Am. J. Pub. Health, to be published.

6. Aureomycin used in this study was furnished by the Lederle Laboratories Division, American Cyanamid Company.

7. These will be referred to as the aureomycin-penicillin group or the combination group.

Throat cultures were made by swabbing tonsillar and posterior pharyngeal regions with sterile cotton swabs, which were immediately plated on sheep-blood agar plates. Nose cultures were similarly obtained, using one swab for both nostrils. Plates were streaked and incubated within an hour of the time they were obtained. One colony of each morphological type of staphylococcus was subcultured and studied for hemolysis on blood agar plates, pigment and coagulase production bacteriophage typing,[8] and penicillin and aureomycin sensitivities. The coagulase test was done by the method of Fisk.[9] The minimal inhibitory concentrations of the antibiotics were determined by the tube dilution method, using a 1:100 broth dilution of an 18-hour culture.

RESULTS

In the presentation of results cultures from the nose and throat have been recorded as separate determinations, but they have been added together in the tables for simplicity of presentation, since the same results were obtained and the same conclusions can be reached concerning the cultures from either region.

TABLE 1.—*Incidence of Positive Nose and/or Throat Cultures for Staphylococci in 357 Patients on Admission and During Hospitalization*

EFFECT OF TREATMENT WITH AUREOMYCIN, PENICILLIN, AND AUREOMYCIN PLUS PENICILLIN

		Positive Cultures*				Cultures Which Were Positive on Admission*				Cultures Which Were Negative on Admission*			
		On Admission		On Discharge		Remained Positive		Became Negative		Became Positive		Remained Negative	
Treatment Group	Total Cultures, No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Penicillin	164	58	35.4	55	33.5	24	41.3	34	58.7	31	29.2	75	70.8
Aureomycin	107	23	21.5	62	57.9	15	65.2	8	34.8	47	55.9	37	44.1
Penicillin plus aureomycin	140	23	16.4	19	13.6	5	21.7	18	79.3	14	12.0	103	88.0
No treatment	122	30	24.6	40	32.8	20	66.7	10	33.3	20	21.7	72	58.3
All patients	533	134	25.1	176	33.0	64	47.8	70	52.2	112	28.1	287	71.9

* Chi-square test revealed the following: 1. The incidence of positive cultures on admission in the penicillin group was significantly higher than that in the aureomycin or aureomycin plus penicillin group (Columns 2 and 3). 2. The incidence of positive cultures at discharge was significantly higher in the aureomycin group than in any other group; the incidence in the aureomycin-penicillin group was significantly lower than in any other group (Columns 4 and 5). 3. The conversion rate from positive to negative cultures in the "no treatment" group was significantly lower than in the penicillin or the aureomcin-penicillin groups; the same rate in the aureomycin group was also significantly lower than that in the aureomycin-penicillin group (Columns 8 and 9). 4. The conversion rate from negative to positive was significantly greater in the aureomycin group than in any other group; the rate for the aureomycin-penicillin group was significantly lower than that for the penicillin group (Columns 10 and 11).

Table 1 shows the incidence of staphylococci found in cultures taken from nares and/or throats of patients in the various treatment groups on admssion to the hospital. Among the 164 initial cultures in the penicillin-treated group 35.4% were positive, and, at the other extreme, only 16.4% of 140 cultures in the penicillin-aureomycin-treated group were positive. The incidence was 21.5% in the aureomycin-treated group and 24.6% of the "no treatment" group. The incidence of positive admission cultures in the penicillin-treated group was significantly higher than in the aureomycin-treated or the combination group; otherwise the differences in distribution were not significant.

Among the patients with positive admission cultures no staphylococci were cultured at the time of discharge in 58.7, 34.8, 78.3, and 33.3% of patients in the

8. Bacteriophages were furnished through the courtesy of Dr. G. B. Leyton, Director of Laboratory Services, Department of Health and Public Welfare, Manitoba, Canada.

9. Fisk, A.: The Technique of the Coagulase Test for Staphylococci, Brit. J. Exper. Path. **21**:311-314, 1940.

penicillin, aureomycin, combination, and "no treatment" groups, respectively. The conversion rate for the "no treatment" group was significantly less than that for either the pencillin or the combination group. Moreover, the conversion rate for the combination group was significantly greater than that of the aureomycin group.

On the other hand, among the patients whose cultures on admission had no staphylococci, positive cultures were obtained by the time of discharge in 29.2, 55.9, 12.0, and 28.1% of the four groups, respectively. This conversion rate among patients receiving penicillin was significantly less than that for the aureomycin group and significantly greater than that for the combination group but was essentially the same as the rate for the "no treatment" group. The conversion rate among the aureomycin-treated patients was significantly higher than that for any other group. The difference between the combination and the "no treatment" groups was not significant.

At the time of discharge, of the cultures obtained from patients who received penicillin 33.5% were positive. This was essentially the same percentage as on admission. In the aureomycin group the incidence of positive cultures had risen

TABLE 2.—*Minimal Concentrations of Penicillin and Aureomycin Required to Inhibit Completely the Growth of Staphylococci Obtained from Nose and Throat Cultures of Patients on Admission*

Minimal Inhibitory Concentration of Penicillin, U./Ml.	Minimal Inhibitory Concentration of Aureomycin, γ/Ml.					Total	
	< 0.12	0.12-0.99	1.00-9.9	10.0-99.9	100.0 and Over	No.	%
< 0.12	7	19	10	2	0	38	45.1
0.12-0.99	1	2	0	0	0	3	3.6
1.00-9.9	0	2	0	1	4	7	8.4
10.0-99.9	0	9	2	1	1	13	15.5
100.0 and over	0	10	12	0	1	23	27.4
Total no.	8	42	24	4	6	84	100.0
Total %	9.5	49.9	28.6	4.8	7.2	100.0	....

significantly by the time of discharge, to 57.9%. Among the combination group only 13.6% had positive cultures, but this was not significantly different from the admission percentage. The 32.8% incidence of positive cultures before discharge in the "no treatment" group also represented no percentage change from that found at the time of admission. The occurrence of positive cultures on discharge was significantly higher in the aureomycin group than in any other group, and the percentage in the combination group was significantly lower than that in any other group.

Table 2 indicates minimal inhibitory concentrations of aureomycin and penicillin required to inhibit 84 strains of staphylococci obtained from patients upon admission. It can be seen that 59.4% were sensitive to 1 γ per milliliter or less of aureomycin and only 12% were resistant to 10 γ per milliliter or more. Forty-five per cent of the organisms were sensitive to less than 0.12 units per milliliter of penicillin and 42.9% required 10 or more units per milliliter of penicillin for inhibition of growth.[10] Thus the staphylococci were either very sensitive or highly resistant to

10. The absolute value given as the inhibitory concentration will vary according to the methods of the test. These tests were all performed by tube dilution with standard inoculation and incubation time.

penicillin, with relatively few organisms in the intermediate range, whereas most of the organisms were rather sensitive to aureomycin and only a few were highly resistant. It was also demonstrated that there was some correlation between the aureomycin and penicillin sensitivities, in that all of the organisms very sensitive to aureomycin (< 0.12 γ per milliliter) were also quite sensitive to penicillin and all of those which required 100 γ per milliliter or more of aureomycin for inhibition were resistant to less than 1 unit per milliliter of penicillin.

Penicillin sensitivities were determined on organisms from 268 cultures obtained from patients shortly before discharge. The distribution of these results is seen in Table 3, and a comparison was made with the distribution observed on the strains from the admission cultures. Nearly half of the initial cultures were inhibited by 1 unit of penicillin per milliliter or less. A significantly lower proportion of the cultures obtained prior to discharge (21%) were inhibited by less than 1 unit per

TABLE 3.—*Minimal Concentrations of Penicillin Required to Inhibit Completely the Growth of Staphylococci Obtained from Final Nose and Throat Cultures Taken Before Discharge: Comparison with Minimal Concentrations Required to Inhibit Staphylococci Obtained from Initial Culture*

	Minimal Inhibitory Concentration of Penicillin, U./Ml.*				
	< 1	1.0-9.9	10.0-99.9	100 and Over	Total
Initial culture	40	10	13	19	82
Discharge culture					
Penicillin	13	1	11	25	50
Aureomycin	12	9	35	20	76
Penicillin plus aureomycin	2	0	5	11	18
No antibiotic	12	10	8	12	42
Total	79	30	72	87	268

* Chi-square test revealed the following: 1. All groups at discharge had a significant decrease in incidence of strains sensitive to less than 1 unit per milliliter below the level on admission (Column 1). 2. All treated groups at discharge had a significant decrease in incidence of strains sensitive to less than 10 units per milliliter compared to the initial level and the "no treatment" group at discharge (Column 2). 3. The incidence of organisms resistant to less than 100 units per milliliter was higher in the penicillin and aureomycin-penicillin groups than the incidence of these on admission or in any other group on discharge; there was no significant difference between the penicillin and combination groups (Column 3).

milliliter, regardless of which drug had been employed or whether any had been used. The incidence of organisms obtained at discharge which penicillin inhibited in a concentration less than 1 unit per milliliter was not significantly different among the four treatment groups.

When 10 units per milliliter was used as a dividing line between sensitivity and resistance, the proportion of "sensitive" organisms in the admission cultures was significantly greater than in the cultures obtained on discharge from patients who had been treated with penicillin, aureomycin, or aureomycin plus penicillin. By this criterion, however, there was no essential difference between the sensitivity of staphylococci obtained from the admission cultures and those obtained before discharge on patients who had received no antibiotic treatment. On the other hand, a significantly greater proportion of staphylococci from admission cultures were inhibited by less than 100 units of penicillin than staphylococci cultured before discharge from patients in either the penicillin or the combination group. Similarly, a significantly higher percentage of the organisms from the penicillin and the combination groups were resistant according to this criterion than were organisms from the aureomycin and "no treatment" groups. There was no significant difference

between the staphylococci obtained from patients in the penicillin and the combination groups when inhibition by 100 γ per milliliter or more was used as a criterion.

The minimal concentrations of aureomycin required to inhibit the 263 strains of staphylococci obtained from patients shortly before discharge is shown in Table 4, compared with the concentrations required to inhibit staphylococci obtained on the "admission cultures." There were significantly more organisms sensitive to 1 γ per milliliter or less of aureomycin from all the initial cultures and from the final cultures from the "no treatment" group than from the final cultures of the penicillin, aureomycin or combination groups, but there was no difference in this respect between the organisms obtained from the initial and final cultures when the patients were not treated with antibiotics. Furthermore, there was a significantly higher percentage of aureomycin-sensitive organisms among cultures from patients treated with penicillin than from those treated with aureomycin. On the other

TABLE 4.—*Minimal Concentrations of Aureomycin Required to Inhibit Completely the Growth of Staphylococci Obtained from Final Nose and Throat Cultures Taken Before Discharge: Comparison with Minimal Concentrations Required to Inhibit Staphylococci Obtained from Initial Culture*

	Minimal Inhibitory Concentration of Aureomycin, γ/ML.*				
	<1	1.0-9.9	10.0-99.9	100 and Over	Total
Initial culture	42	24	5	8	79
Discharge culture					
Penicillin	14	14	10	11	49
Aureomycin	6	8	23	39	76
Penicillin plus aureomycin	1	2	5	10	18
No antibiotic	21	9	7	4	41
Total	84	57	50	72	263

* Chi-square test revealed the following: 1. Incidence of organisms sensitive to 1 γ per milliliter or less was significantly greater in the initial culture and in the "no treatment" group than in any other group; there was no difference between the initial cultures and the "no treatment" group; there were significantly more sensitive strains in the penicillin-treated group than in the aureomycin-treated group (Column 1). 2. Incidence of organisms sensitive to 10 γ per milliliter or less was significantly higher in the initial cultures than in any group except the "no treatment" group; it was higher in the penicillin and "no treatment" groups than in the aureomycin or aureomycin-penicillin group (Column 2). 3. Incidence of organisms sensitive to 100 γ per milliliter or less was significantly greater in the initial cultures and the penicillin and "no treatment groups than in the aureomycin and aureomycin-penicillin groups (Column 3).

hand, there was no significant difference between staphylococci from the combination group and either of the other antibiotic groups.

When a minimal inhibitory concentration of 10 γ per milliliter was used as a separating point, again there were significantly more sensitive strains in the initial cultures than in the discharge cultures obtained from any of the groups except the "no treatment" group. There were also more sensitive strains among those obtained from the penicillin patients than among those obtained from either the aureomycin or combination group. Fewer sensitive strains were cultured from either of the latter groups also than from the "no treatment" patients. There was no significant difference between the staphylococci from the aureomycin and combination groups.

When 100 γ per milliliter was used as a dividing line, a significantly higher proportion of resistant staphylococci was obtained from cultures from patients in the aureomycin and combination groups than from the cultures obtained prior to treatment or from cultures from penicillin-treated or "no treatment" patients. Strains obtained from the latter three groups did not differ among themselves

according to this criterion, nor were those obtained from the aureomycin group significantly different from the strains cultured from the combination group.

The sensitivities of the staphylococci from the nose and throat of the personnel were studied during and at the end of this study. Table 5 shows the distribution of aureomycin and penicillin sensitivities among the organisms obtained from the nose and/or throat of personnel at the end of the study. Since there was no difference between those from the nose and those from the throat, they were tabulated together. In this distribution there was a heavy concentration of organisms which

TABLE 5.—*Minimal Concentrations of Aurtomycin and Penicillin Required to Inhibit Completely the Growth of Staphylococci Obtained from Hospital Personnel at End of Study Period*

Minimal Inhibitory Concentration of Penicillin, U./Ml.	Minimal Inhibitory Concentration of Aureomycin, γ/Ml.					Total	
	< 0.12	0.12-0.99	1.00-9.9	10.0-99.9	100.0 and Over	No.	%
< 0.12	1	0	2	1	0	4	7.9
0.12-0.99	0	1	0	0	1	2	3.9
1.00-9.9	0	2	4	1	10	17	33.3
10.0-99.9	0	0	5	0	7	12	23.5
100.0 and over	0	1	4	3	8	16	31.4
Total no.	1	4	15	5	26	51	....
Total %	2.0	7.9	29.4	9.8	51.0	..	100.0

TABLE 6.—*Change in Distribution of Staphylococci Obtained from Personnel and Patients During the Course of the Study According to the Minimal Inhibitory Concentration of Aureomycin*

	Total Cultures, No.	Minimal Inhibitory Concentration of Aureomycin, γ/Ml.									
		< 0.12		0.12-0.99		1.00-9.9		10.0-99.9		100.0 and Over	
		No.	%	No.	%	No.	%	No.	%	No.	%
Personnel											
December 1951	30	0	0	7	23.3	13	43.4	2	6.7	8	26.7
April 1952	51	1	2.0	4	7.8	15	29.4	5	9.8	26	51.0
Patients											
July-September 1951	25	8	32.0	13	52.0	1	4.0	1	4.0	2	8.0
October 1951-January 1952	34	2	5.9	13	38.2	14	41.2	1	2.9	4	11.8
February-April 1952	26	0	0	15	57.7	5	19.3	3	11.5	3	11.5

were relatively resistant to both antibiotics as compared with those from hospital patients on admission or even at the time of discharge.

Although there was no difference in the distribution of pencillin sensitivities between the mid-study and end-study cultures from the personnel, Table 6 illustrates that there was a marked increase in resistance to aureomycin, particularly with respect to the frequency of highly resistant strains.

Table 6 also illustrates that there was some increase during the period of the study in the number of staphylococci in the community which were resistant to aureomycin; in particular, the strains which were inhibited by less than 0.12 γ per milliliter tended to disappear from the nares and throats of the patients. There was no change in the distribution of pencillin sensitivities during the study.

In order to see how much of the above data can be explained on the basis of the spread of organisms between the patients and the personnel, several calculations have been made.

In Table 7 the actual number of organisms found to be sensitive to different concentrations of penicillin and aureomycin in the different treatment groups presented in Tables 3 and 4 are compared with "expected" values. The "expected" values were computed, using a patient : personnel ratio of 100 to 80 and using the antibiotic sensitivities as found on the organisms obtained from the patients on admission (Table 2) and on the personnel, as recorded in Table 5. If a complete mixing of the organisms from the noses and throats of the personnel to the patients is assumed, the expected distribution of penicillin and aureomycin sensitivities agrees quite well with that actually found among the "no treatment" group.

Similarly, when one assumes penicillin to be 80% effective in eradicating from the nares and throats of patients and preventing implantation in them of organisms sensitive to 0.1 units per milliliter or less, the "expected" and actual figures agree closely. A similar assumption for aureomycin at the 1 γ per milliliter level of activity gives reasonable agreement between the "expected" and observed results.

TABLE 7.—*Actual and Expected Distribution of Strains of Staphylococci Isolated from Nose and/or Throat of Patients on Discharge According to the Minimal Inhibitory Concentrations of Penicillin and Aureomycin*

	Penicillin Sensitivity of Strains				Aureomycin Sensitivity of Strains			
	< 1 U./Ml.		> 100 U./Ml.		< 1 γ/Ml.		> 100 γ/Ml.	
Treatment Group	Actual, No.	Expected,* No.	Actual, No.	Expected,* No.	Actual, No.	Expected,* No.	Actual, No.	Expected,* No.
Penicillin	13	9	25	30	14	15	38	32
Aureomycin	12	10	56	42	6	7	37	36
Penicillin plus aureomycin	2	2	7	8	1	1	8	8
No treatment	12	14	30	32	21	18	37	35

* The estimates are based on the assumptions of free exchange of staphylococci between personnel and patients, ratio of patients to personnel 100:80, and penicillin 80% effective against organisms sensitive to 0.1 unit per milliliter or less and aureomycin 80% effective against organisms sensitive to 1.0 γ per milliliter.

The latter figures are based on Table 6 rather than on Table 5, since these figures were obtained nearer the middle of the study and are more likely to reflect the average for the personnel during the study.

When both antibiotics were used, each was assumed to be 80% effective at the expressed levels of sensitivity of either alone. Again, there was fair agreement between "expected" and demonstrated figures.

Somewhat similar treatment of the material gave information of interest as tabulated in Table 8. The following calculations were made in order to estimate the conversion of cultures expected to be converted from negative to positive. Using the same assumptions as above, it was calculated that in the "no treatment" group 42% of the patients were exposed to staphylococci and only 21% had the organism implant long enough for it to be demonstrated. The expected rate of implantation was therefore considered to be one-half of the exposure rate. When these figures are used, there is fair agreement of what actually occurred with the expected rate of occurrence except in the aureomycin-treated group. The expected conversion rate from positive to negative cultures was calculated in the following manner: The rate of conversion for the "no treatment" group was assumed to be the natural rate. The values for the various antibiotic-treated groups were calculated by adding this rate to the rates expected to result from the assumed thera-

peutic effect of the drug. The latter effect was based on an 80% effect at the sensitivities specified above, from which was subtracted a reimplantation rate computed from the actual negative to positive conversion rate. These calculated rates agreed well with the experimentally determined ones.

Oxytetracycline was given to eight patients, not included among the above, from whom staphylococci were obtained on discharge. In all of these patients the organism obtained at the time of discharge was relatively resistant to both aureomycin and oxytetracycline.

COMMENT

The results obtained in this study agree well with those in the literature, which indicate that patients in the hospital more frequently become carriers of penicillin-resistant staphylococci than members of the population as a whole, that the hospital personnel serve as transmitters of these organisms, and that the number of staphylococci resistant to aureomycin is increasing by a similar mechanism.

TABLE 8.—*Expected and Actual Change in the Occurrence of Staphylococci in Nose and Throat Cultures from Hospital Patients*

Treatment Group	Positive Cultures on Admission Which Later Became Negative, No.		Negative Cultures on Admission Which Later Became Positive, No.	
	Expected*	Actual	Expected*	Actual
Penicillin	29.0	34	19.8	31
Aureomycin	11.1	8	17.6	47
Penicillin plus aureomycin	15.9	18	14.0	14
No treatment	....	33.3%	....	21.7%

* The estimates are based on the assumptions of free exchange of staphylococci between personnel and patients, ratio of patients to personnel 100:80, and penicillin 80% effective against organisms sensitive to 0.1 unit per milliliter or less and aureomycin 80% effective against organisms sensitive to 1.0 γ per milliliter.

It would seem that the excellent agreement of the experimental results with the hypothetical distribution based on the samples involved indicates that almost all significant changes as to conversion rates from negative to positive cultures and vice versa and the distribution of antibiotic sensitivities at the time of discharge can be explained in terms of free interchange of staphylococci between personnel and patients. The exception to such an agreement of results is the extremely high negative to positive conversion rate in the aureomycin group. This conversion rate may depend in part on the fact that aureomycin has greater effectiveness against the Gram-negative rods than penicillin but a lower effectiveness against some staphylococci than the combination of aureomycin and penicillin. The latter depends on the incidence of penicillin-sensitive aureomycin-resistant strains in the population. These factors may have encouraged a higher implantation of staphylococci in the aureomycin-treated group than in the other groups.

From the good agreement between the expected and actual results obtained in Table 7 it would seem that no explanation for the increase in the proportion of resistant strains of staphylococci in hospitalized patients is necessary other than the transfer of resistant strains from patients to personnel and from personnel to patients, especially those receiving antibiotics.

Obviously, the answer to the problem of development of antibiotic resistance of an individual strain while the host is receiving the antibiotic must be based on

study of the individual strains. This portion of our study is as yet incomplete. From the data accumulated thus far it appears that when a patient harbored staphylococci which varied widely in their sensitivity to aureomycin or penicillin at different times, the strains were found to be different organisms. These findings lend further support to the hypothesis that the major cause for the increased proportion of resistant strains which we observed as the study progressed was the implantation of resistant strains from the personnel. Because of this fact the exact quantitative findings of this study might not be applicable to a different environment where the values of the variables were different. Nevertheless, the following hypotheses may be tentatively advanced in an attempt to apply the present findings to the problem of the community at large.

1. An area in which large numbers of patients are treated with antibiotics at the same time is apt to become a nidus of infection with antibiotic-resistant staphylococci. From such an area patients may at times transmit them into the community after their discharge from the hospital.

2. Such a nidus of infected personnel will infect persons who are not receiving antibiotics but not to the same extent as patients in whom the more sensitive strains are removed by antibiotic treatment.

3. In the community as a whole, where the effects of several such foci are diluted by the remainder of the population, antibiotic-resistant strains may appear more slowly. In such instances a slow increase in the percentage of resistant forms could occur without actual increase in resistance occurring in any single strain while patients are being treated.

4. It is possible that if there were any resistant strains in the community at all when a new antibiotic is introduced, even if there were no change in the sensitivity of any individual strains, a process of selective survival of the existing resistant strains could in time produce a predominantly resistant population.

5. Combination of aureomycin and penicillin in treatment will limit the spread of organisms sensitive to one antibiotic and not to the other but will increase the spread of organisms resistant to both, if such organisms exist. It is likely in time that a nidus of these organisms would be established and the combination would then have lost its value.

SUMMARY

A study of the epidemiology of the carrier state of penicillin- and aureomycin-resistant staphylococci in patients in one hospital has been made. Two hundred sixty-eight strains of staphylococci obtained from the nares and throats of 357 patients and 51 strains from the nares and throats of 72 members of the hospital personnel were utilized.

It was shown that untreated patients in this environment had a higher carrier rate at the time of discharge than on admission and that they had an increase in the percentage of organisms resistant to one unit per milliliter of penicillin and no change in the distribution of sensitivity to aureomycin. Patients treated with penicillin showed no change in carrier rate, but when staphylococci were present there was a significant increase in the proportion of strains resistant to less than 100 units per milliliter of penicillin and to less than 10 γ per milliliter of aureomycin during hospitalization. Patients treated with aureomycin had a marked increase in

carrier rate and a significantly higher percentage of organisms resistant to 10 units per milliliter of penicillin and 100 γ per milliliter of aureomycin than was found in the initial culture. Patients treated with aureomycin plus penicillin had no essential change in carrier rate. However, there was a significant increase in the percentage of organisms resistant to less than 100 units per milliliter of penicillin and to less than 100 γ per milliliter of aureomycin.

All the observed phenomena can be explained in terms of a free interchange of organisms between patients and personnel and personnel and patients, with consideration of the effect of antibiotics on the sensitive strains.

During the time of the study, July, 1951, to April, 1952, there was a significant increase of the number of staphylococci which were resistant to aureomycin in the community and, to a greater extent, among hospital personnel.

Studies on eight patients who received oxytetracycline revealed that the results were similar to those obtained with aureomycin.

Certain implications of this study are discussed.

Mrs. Gayle Pierzinski Hager and Miss Anne Rurka gave technical help in this study.

DESCRIPTIVE CHARACTERISTICS OF GROUP OF PATIENTS WITH MODERATE OR SEVERE DIABETIC ACIDOSIS

Relation to Recovery or Death

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THE PRESENT study is in essence a systematic characterization of a sample of patients with diabetic acidosis who were observed and treated on a representative alert medical service. Our objective is to record observations on a relatively unselected group of patients with diabetic acidosis, such as one might encounter in any teaching hospital where no special emphasis is placed on the study of such patients. These cases reflect the customary approach to diagnosis and therapy, not necessarily the best approach. We are describing things as they are, not as they might be. The group includes the available cases of moderate or severe acidosis as recorded in a given medical service's hospital charts.

Various well-known clinical surveys of diabetic acidosis or coma have appeared in the past.[1] However all of them have followed more or less similar patterns of analysis and have restricted their scope to certain prominent items of interest, such as precipitating factors and complications, age, sex, duration of diabetes, mental state, blood sugar, carbon-dioxide-combining power, blood urea nitrogen, and total amount of insulin required. The influence of variations in these factors on mortality has been of primary concern.

In the present instance, all available information was recorded and systematically analyzed in order to typify the groups with respect to each item of information. The factual data fell naturally into five descriptive categories: (1) general characteristics of the patients, (2) clinical characteristics of the acidosis, (3) laboratory characteristics of the acidosis, (4) treatment received, and (5) response to treatment. Within this framework 61 descriptive variables are evaluated in the analysis that follows.

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METHODS AND MATERIALS

Criteria for Selecting Cases for Study.—In reviewing records of diabetic patients for purposes of selecting all cases having sufficiently severe acidosis, one desires to avoid the error of including cases with mild acidosis or of excluding cases with moderate or severe acidosis. In the past it has been customary to define moderate or severe acidosis, for review purposes, in terms of the carbon-dioxide-combining power alone. Thus, for example, Dillon and Dyer [1b] restricted themselves to cases below 30 vol. %, Baker,[1a] to cases below 25 vol. %, and Joslin and his associates [1f] to cases below 20 vol. %. Of the usual determinations, the CO_2-combining power indicates best the existence of acidosis, distinguishing the normal from the acidotic diabetic very well and enabling a precise standard of classification to be set up. Though precise, the levels chosen to distinguish a moderate or severe case of acidosis from a mild one have been arbitrary and have predisposed somewhat to errors of exclusion. Below approximately 40 vol. % the CO_2 does not correlate perfectly with the severity of the patient's condition as evidenced by the clinical state or by survival figures and it is of but limited predictive value in distinguishing intermediate grades of severity in this region. In essence, the CO_2 is a good diagnostic measure but an unsatisfactory prognostic measure. Though nearly all cases with CO_2 below 30 vol. % are probably correctly classified as moderate or severe, some with CO_2 between 30 and 40 vol. % also fall into this category by clinical criteria. In order not to omit these cases, it would seem highly desirable when estimating severity to take into account, in addition to the rise in blood sugar and drop in CO_2, the major clinical factors indicating the existence of moderate or severe acidosis. Thus, for example, a semiconscious dehydrated diabetic with lowered blood pressure, hyperglycemia, and acetonuria whose admission CO_2 combining power was 38 vol. % died in deep coma despite therapy.

In reviewing the hospital charts for purposes of assembling the cases utilized in the present analysis, any acidosis in which the admission CO_2 was less than 30 vol. % was accepted as more than mild. In addition, patients with CO_2 between 30 and 40 vol. % (and one with admission CO_2 of 46 vol. % which shortly dropped to 12 vol. %) who were semiconscious or unconscious or who had hypotension or azotemia or any combination of these findings were similarly classified and accepted for study.

Case Material.—Records of all cases of diabetic acidosis seen at the University Hospitals between 1930 and 1948 and at the Veterans Administration Hospital between 1946 and 1948 were reviewed, and detailed descriptive information was tabulated for each case wherever available. There were 124 charts containing sufficient information to enable the diagnosis of moderate or severe diabetic acidosis to be made. The patients represented formed two groups, 88 who recovered and 36 who died. Instances of multiple episodes of acidosis were available; however, for this analysis, a given case was utilized but once. Several patients were excluded whose deaths were definitely known to be due to an associated condition, the acidosis being incidental. All patients with admission CO_2 over 30 vol. % who later died had autopsies showing no organic abnormality to account for the death. These were presumed to be "biochemical deaths." Resident physicians, under the supervision of a staff physician, were responsible for the care and treatment of these patients.

Descriptive Variables.—The variables fitted into one of five descriptive categories, and the analyzed data have been assembled in five tables, one corresponding to each category. Most of the variables and their units of measurement are self-explanatory in the tables. Unless otherwise designated, all clinical and test data are values obtained on admission to the hospital. A few items require special comment.

Mean blood pressure (systolic + diastolic) 2, was utilized in preference to either systolic or diastolic pressure alone. It reflects both. "Previous episodes" in Table 1 refers to previous episodes of moderate or severe acidosis. Duration of decreased sensibility was estimated from symptoms elicited and relatives' descriptions of the patient's behavior. The estimates are at best approximate, yet cannot be ignored. Degree of unconsciousness was rated on a five-point scale: 1, drowsy; 2, semiconscious; 3, unconscious but responsive to pain; 4, unconscious and unresponsive. A rating of 0 indicated that the patient was conscious and alert. Associated conditions were rated on a six-point scale: 1, very mild; 2, mild; 3, moderately severe; 4, severe; 5, very severe. A rating of 0 indicated none was present. An infection, besides being included as an associated condition, was rated separately in similar fashion.

Information concerning items of therapy was recorded at 3, 6, 12, and 24 hours after admission to the hospital. Only therapy given parenterally was amenable to analysis. In evaluating figures representing the amount of dextrose given parenterally it should be recognized that this institution's policy has not been to give dextrose along with insulin early during therapy. Dextrose has generally been withheld until appreciable response to therapy has occurred. It was used primarily as a cushion against hypoglycemia. The recorded figures for alkali given represent equivalents in terms of sodium bicarbonate, though ⅙ molar lactate was also given. The 24-hour alkali figures for the group that died include values for all cases, even though, some deaths occurred before the end of the 24-hour period.

Analysis.—Average values were calculated, where appropriate, for each item in each of the two major groups, those who lived and those who died. Variations about these means were represented by standard deviations and ranges. Where useful, percentage incidence of certain values of a variable were calculated. As might be expected, many items were incompletely recorded in the clinical records. The analysis of any given item was thus restricted to those cases in which information was available. The number of cases utilized in the calculations with each item is therefore recorded.

For each variable, comparisons were made between those who recovered and those who died. A difference between groups that is statistically significant is indicated in the tables by an asterisk between the means or percentages compared. In testing the significance of differences between means, each difference was compared with its standard error. Chi-square was used in testing the significance of differences between percentages.

RESULTS AND INTERPRETATIONS

General Characteristics of the Patients.—Table 1 summarizes the information available on 11 items falling in this category.

Somewhat over twice as many patients were treated in the 1940's as in the 1930's. The average age of the group as a whole was 36.6 years, with a range of 11 to 77 years. This may be compared with Harwood's [2] series, in which the average age was 36 years and the range 14 to 75 years, and with Dillon and Dyer's [1b] series, in which the average age was 37.8 years. Those who died were, on the average, much older than those who survived. Two-thirds of the latter were under 30, whereas nearly two-thirds of those who died were 50 or older. The average age of those who survived was approximately 30 and of those who died 53. This compares with the corresponding figures of 30 and 48, respectively, observed by Dillon and Dyer.

The sex distribution of this series, 43.5% males and 56.5% females, is identical with that observed by Baker [1a] and intermediate between those reported by Collen [3] (38% males, 62% females) and Harwood (49% males, 51% females). Dillon and Dyer's percentages were 30% males and 70% females. The mortality among men in Collen's series was 34% and among women 33%. In the present series these mortality percentages are 24 and 33, respectively.

Those in the group that died weighed more, on the average, than those in the group that recovered. The members of both groups weighed less than usual at the time of admission in acidosis.

In keeping with the facts that they were older and weighed more, those who died manifested a significantly higher average blood pressure prior to their acidosis. The case records were quite incomplete on this point, however.

2. Harwood, R.: Diabetic Acidosis: Results of Treatment in 67 Consecutive Cases, New England J. Med. **245**:1-9, 1951.

3. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med. **70**:347-368, 1942.

Diabetes had been present an average of 5.4 years prior to the episode of acidosis. In the studies of Joslin and his associates [4] the average duration was 5.5 years. The corresponding figure for only those who died was observed to be 4.0 years by Joslin and was 4.4 years in the present survey. One-third of those who died, in contrast to one-tenth of those who recovered, did not know that they had diabetes prior to the episode of acidosis. For the entire group the percentage was 17.2. This is comparable to the values of 20.5% observed by Beardwood and Rouse [1e] and 23% observed by Harwood.

TABLE 1.—*General Characteristics of Patients with Diabetic Acidosis*

	Patients Who Lived	Patients Who Died	All Patients
Decade treated			
Patients, no.	88	36	124
1930-1939, %	26.1	36.1	29.0
1940-1948, %	73.9	63.9	71.0
Age, yr.			
Patients, no.	88	36	124
Mean	29.9*	52.9	36.6
S. D.†	15.9	16.6	19.2
Range	11-68	18-77	11-77
Under 30, %	67.1*	13.9	51.6
30-49, %	13.6	22.2	14.5
50 or over, %	19.3	63.9	33.9
Sex			
Male, %	46.6	36.1	43.5
Female, %	53.4	63.9	56.5
Race			
Not white, no.	0	2	2
Height, in.			
Patients, no.	50	27	77
Mean	65.9	64.9	65.5
S. D.	4.3	3.8	4.2
Range	55-74	59-71	55-74
Usual weight, lb.			
Patients, no.	68	10	78
Mean	133*	157	136
S. D.	28	32	29
Range	72-195	124-220	72-220
Adm.† Weight, lb.			
Patients, no.	73	26	99
Mean	123*	149	130
S. D.	25	35	30
Range	66-178	80-250	66-250
Usual B. P.†			
Patients, no.	41	7	48
Mean	95.1*	112.6	97.7
S. D.	13.8	9.1	14.5
Range	58-133	85-140	58-140
Dur.† diabetes, yr.			
Patients, no.	88	34	122
Mean	5.82	4.38	5.42
S. D.	5.02	5.87	5.28
Range	0-23	0-25	0-25
Duration 0, %	10.2*	35.3	17.2
Daily insulin, units			
Patients, no.	86	33	119
Mean	37.1*	11.4	30.0
S. D.	27.5	19.4	27.9
Range	0-120	0-70	0-120
None, %	22.1*	66.7	34.5
Previous episodes			
Patients, no.	85	35	120
None, %	60.0*	91.4	69.2
One or two, %	24.7	2.9	18.3
More than two, %	15.3	5.7	12.5

* Statistically significant difference between the groups.
† Abbreviations are as follows: S. D., standard deviation; Adm., admission; B. P., blood pressure (systolic + diastolic)/2; Dur., duration of.

The incidence of patients not taking insulin was approximately twice the incidence of undiagnosed cases. Thus two-thirds of those who died and one-fifth of those who survived were not receiving insulin before admission. This discrepancy accounts for the lower average insulin dosage received by those who died in acidosis.

There was a similar marked difference between those who lived and those who died in the number having previous episodes of acidosis. Of the former, 40% had one or more episodes; whereas, of the latter only 9% had one or more episodes. It is evident from this, as well as from the preceding two items of analysis, that persons without previous knowledge of or experience with diabetes are less apt to be aware of significant symptoms and of the hazards of delay and neglect.

4. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, Ed. 8, Philadelphia, Lea & Febiger, 1946.

Clinical Characteristics of the Acidosis.—Twelve items of information were analyzed under this heading (Table 2).

The average duration of decreased sensibility and responsiveness was 3.9 hours for those who lived and 11.5 hours for those who died. Three-fourths of the former were alert on admission; only 18% of those that died were alert.

TABLE 2.—*Clinical Characteristics of Acidosis*

	Patients Who Lived	Patients Who Died	All Patients
Decr. sensibility,† hr.			
Patients, no.	88	33	121
Mean	3.86*	11.49	5.94
S. D.†	14.14	13.63	14.28
Range	0-120	0-48	0-120
None, %	75.0*	18.2	59.5
1-12, %	19.3	54.6	28.9
Over 12, %	5.7	27.3	11.6
Degree unconsciousness			
Patients, no.	88	36	124
Mean	1.52*	2.50	1.81
S. D.	1.16	0.85	1.17
Range	0-4	0-4	0-4
Con. or semicon,† %	79.5*	55.6	72.6
Unconscious, %	20.5	44.4	27.4
Hr. since onset vomiting			
Patients, no.	86	24	110
Mean	27.6	35.4	29.3
S. D.	39.0	48.9	41.2
Range	0-168	0-168	0-168
None, %	32.6	45.8	35.5
Bloody or coffee vomitus			
Present, %	10.3	3.6	8.7
Min. temp.,† 1st 3 hr.			
Patients, no.	84	35	119
Mean	98.8*	97.9	98.6
S. D.	1.5	2.5	1.9
Range	94.0-102.2	93.2-102.4	93.2-102.4
Max.† pulse, 1st 3 hr.			
Patients, no.	84	31	115
Mean	115	112	114
S. D.	16	27	19
Range	80-160	60-170	60-170
Max, resp.,† 1st 3 hr.			
Patients, no.	81	32	113
Mean	26.1*	31.5	27.6
S. D.	6.6	10.7	8.3
Range	14-56	16-60	14-60
Admission B. P.†			
Patients, no.	87	35	122
Mean	99.6*	75.5	93.0
S. D.	16.6	37.4	26.2
Range	60-162	0-141	0-162
Below 70, %	4.6*	33.3	13.1
Min. B. P., 1st 6 hr.			
Patients, no.	83	26	109
Mean	93.7*	55.6	84.6
S. D.	17.2	30.5	26.5
Range	0-148	0-115	0-148
Below 70, %	6.0*	61.5	19.3
Associated condition			
Patients, no.	88	36	124
Mean	0.77*	2.47	1.27
S. D.	1.13	1.63	1.50
Absent or mild, %	89.8*	50.0	78.2
Mod. or severe, %	10.2	50.0	21.8
Infection			
Patients, no.	88	36	124
Mean	0.88*	2.22	1.27
S. D.	1.18	1.79	1.51
Absent or mild, %	90.9*	58.3	84.2
Mod. or severe, %	9.1	41.7	15.8
Anuria or oliguria			
Patients, no.	88	31	119
Anuric, %	2.3*	25.8	8.4
Mean hr. anuric	5.50	9.63	8.80
Anuric or oliguric, %	8.0*	54.8	20.2

* Statistically significant difference between the groups.
† Abbreviations are as follows: Decr. sensibility, duration of decreased sensibility; S. D., standard deviation; Con. or semicon, conscious or semiconscious; Min. temp., minimum temperature; Max., maximum; resp., respiration rate; B. P., blood pressure.

The state of consciousness was ranked on a five-point scale, from 0 to 4, the last four ratings representing various degrees of cerebral depression. The average rating for those who died was significantly higher. One-fifth (21%) of those who lived and slightly over two-fifths (44%) of those who died were unconscious at the time of admission. This corresponds to the finding of Danowski, Winkler, and Peters [5] that 21% of those who lived and 38% of those who died were in coma. Of the total group 73% were conscious or semiconscious and 27% were unconscious. In the series presented by Dillon and Dyer, of 268 admissions, 70% of the patients

5. Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Salt Depletion, Peripheral Vascular Collapse, and the Treatment of Diabetic Acidosis, Yale J. Biol. & Med. **18**:405-417, 1946.

were conscious and 30% unconscious. They also observed that 28% of their conscious patients and 81% of their unconscious patients died. In the present group a comparable percentage (22%) of the conscious patients died; however, only 47% of the unconscious patients died.

An average of approximately 30 hours elapsed between the onset of vomiting and admission to the hospital. However, about one-third (36%) of the patients had no vomiting, a figure agreeing well with Baker's observation that vomiting was absent in 33% of his series. The differences between those who lived and those who died were not significant. Less than one-tenth of the group had bloody or coffee-ground vomitus. Here again, the two subgroups were similar.

Extreme changes in temperature, pulse, and respirations during the first three-hour period of hospitalization were recorded. The minimum temperature ranged from 93.2 to 102.4 F. The average value was significantly lower for the group that died. Similarly, the maximum respiratory rate varied from 14 to 60 per minute, and the average value (31.5) for those who died was significantly higher than for those who recovered. The average maximum pulse rate was 114 per minute and did not vary appreciably between the groups.

The mean blood pressure (the average of the systolic and diastolic values, in millimeters of mercury) was recorded for each patient. A value of 100 corresponds to a systolic pressure of 120 and a diastolic of 80. Similarly, a value of 70 corresponds to a systolic pressure of 80 and a diastolic of 60. The average admission pressure for those who recovered was approximately 100 and for those who died 75. One-third of those who died were in shock (i. e., mean pressure below 70) on admission, in contrast with one-twentieth of those who lived. The mortality rate for those with a mean pressure below 70 was 75%. Collen observed a mortality rate of 72% among his patients with systolic pressures below 90. More marked differences between the groups of those who lived and of those who died are evident in the figures for minimum blood pressure recorded in the first six hours after admission. The average value for those who recovered was 94 and for those who died 56. Proportionately, 10 times as many patients who died reached shock levels during the first six hours.

A ranking of severity of associated conditions was made, utilizing a six-point scale of which the last five ratings represented varying grades of severity. The average rating for those who died was approximately three times that of the survivors. One-half of those who died, in contrast with one-tenth of those who recovered, had a moderate or severe complicating condition. Ninety-seven of the 124 patients had no complicating disease or had one that was mild. Twenty-seven had moderate or severe complicating diseases. The mortality rate among the former was 18.6%, among the latter, 66.7%. Dillon and Dyer observed mortality rates of 24.8% among those with no associated condition and 61.2% among those with mild to severe complicating diseases. Corresponding mortality figures of 16.8% and 71.5%, respectively, were noted by Collen.

Complicating infections, which were included under the previous category, were also analyzed separately in analogous fashion. The results were similar to those noted above for associated conditions in general.

Oliguria or anuria was present in one-fifth of the patients as a whole. It existed in over half of those who died and in 8% of those who lived. One-fourth of the former were completely anuric, whereas 2% of the latter were. Anuria, when present, was more prolonged among those who died.

Laboratory Characteristics of the Acidosis.—Data concerning nine laboratory determinations are presented in Table 3.

Admission blood sugar values ranged from 188 to 1,165 mg. per 100 cc. The difference between the mean values of the two groups was approximately 100 mg. per 100 cc., a significant difference. The average blood sugar among the patients who recovered in the series of Dillon and Dyer was 478 mg. per 100 cc. (in the present series, 506 mg. per 100 cc.) and among those that died, 567 mg. per 100 cc. (in the present series, 616 mg. per 100 cc.). Approximately 15% of the present group had blood sugar values over 800 mg., and 7% had values over 1,000 mg. per 100 cc.

TABLE 3.—*Laboratory Characteristics of Acidosis*

	Patients Who Lived	Patients Who Died	All Patients
Blood sugar, mg./100 cc.			
Patients, no.	88	36	124
Mean	506*	616	533
S. D.†	223	183	223
Range	188-1076	335-1165	188-1165
Over 800, %	13.6	16.7	14.5
Over 1,000, %	4.6	11.1	6.5
CO_2,† vol. %			
Patients, no.	86	35	121
Mean	20.5	20.2	20.4
S. D.	7.6	10.2	8.4
Range	10-37	8-4	8-46
Under 25, %	68.6	71.4	69.4
25 or above, %	31.4	28.6	30.6
BUN,† mg./100 cc.			
Patients, no.	57	29	86
Mean	23.7*	45.3	31.0
S. D.	14.7	23.2	20.6
Range	7-90	12-109	7-109
Under 30, %	80.7*	27.6	62.8
30 or above, %	19.3	72.4	37.2
Chloride, mg./100 cc. NaCl			
Patients, no.	31	9	40
Mean	590	598	592
S. D.	49	76	53
Range	522-718	480-672	480-718
WBC,† thousands			
Patients, no.	84	27	111
Mean	16.5	17.5	16.9
S. D.	9.0	8.4	8.8
Range	4.2-48.0	4.7-35.2	4.2-48.0
PMN † leukocytes, %			
Patients, no.	82	25	107
Mean	77.9*	83.1	79.1
S. D.	10.0	7.5	9.7
Range	53-94	67-98	53-98
Admission Hb,† gm./100 cc.			
Patients, no.	81	23	104
Mean	13.9	14.0	13.9
S. D.	2.1	2.0	2.1
Range	9.2-16.9	10.5-22.2	9.2-22.2
Urine acetone			
Patients, no.	88	35	123
None, %	3.4	2.9	3.3
Urine diacetic acid			
Patients, no.	85	34	119
None, %	16.5*	41.2	23.5

* Statistically significant difference between the groups.
† Abbreviations are as follows: S. D., standard deviation; CO_2, carbon-dioxide-combining power; BUN, blood urea nitrogen; WBC, white blood cells; PMN, polymorphonuclear; Hb, hemoglobin.

There was no difference between the group of patients who lived and the group of patients who died in the CO_2-combining power. The average for each was 20 vol. %. This corresponds to the results of Dillon and Dyer, in which the average was 19 vol.% for each. The present analysis revealed 37 patients (31%) with CO_2 at or above 25 vol.%. Their average value at admission was 31 vol.%. The study made by Beardwood and Rouse included 102 patients (46%) with CO_2 over 20 vol.%, whose average value at admission was 30 vol.%. In the present series 27% of those with CO_2 values below 25 vol.% and 30% of those with values at or above this level died in coma. In Collen's series 33% of those with CO_2 values below 20 vol.% and 33% of those with values at or above this level died in coma.

A marked discrepancy between the survival groups was noted in blood urea nitrogen. The average for those who lived was 24 mg. and for those who died, 45 mg. per 100 cc. Dillon and Dyer observed average values of 21 and 40 mg. per 100 cc., respectively. They also noted that 22% of those with values below 20 mg. per 100 cc. and 62% with values above this level died. In comparison, 15% of the present sample with blood urea nitrogen below 30 mg. per 100 cc. and 65% with blood urea nitrogen above this level died in coma. The two series are thus in one more respect surprisingly similar. This association between mortality and azotemia is evident again when survival is the primary criterion of classification. Thus, over 80% of those who lived had blood urea nitrogen below 30 mg. per 100 cc., whereas over 70% of those who died had blood urea nitrogen exceeding this level.

At admission chloride and hemoglobin concentrations were sometimes lower (loss or deficiency) and other times higher (hemoconcentration) than normal, the average being approximately normal.

The patients showed a mild leucocytosis, similar in the two groups, though the neutrophilia was more pronounced in those who died, probably owing to associated infections.

Only 3% of either group was without acetone in the urine. Seventeen per cent of those who lived had no diacetic acid in their urine, probably in some because of the moderate nature of their acidosis and in others because of its severity (impaired renal function). In contrast, 41% of those who died had no diacetic acid in their urine, probably primarily because of the marked renal impairment.

Treatment Received.—Table 4 summarizes six treatment items recorded cumulatively at four time intervals (3, 6, 12, and 24 hours).

On the average, those who died and those who lived received approximately similar amounts of insulin at each time interval, though a tendency for the former group to have received larger amounts after the critical initial three-hour period is evident. The average amount of insulin received in 24 hours by those who lived was 216 units; that received by those who died was 252 units. These dosages are similar to those reported in the review of Danowski and his associates, in which 205 and 246 units, respectively, were given in 24 hours. For the entire group an average of 220 units was given in 24 hours, a figure to be compared with Joslin's average of 225 units, based on 651 cases.

The parenteral fluids given these patients were generally isotonic sodium chloride or ⅙ molar lactate and occasionally plasma, sodium bicarbonate, or dextrose in water. Those with the more serious illnesses received more fluids, particularly after the first six-hour period. The average amount received at the end of six hours was 2.5 liters for those who recovered and 3.0 liters for those who died. Correspondingly, the amounts received in 24 hours were 4.2 liters and 6.5 liters, respectively. A similar pattern is naturally observed when the amount of sodium chloride received is the variable under consideration. In 24 hours an average of 27 gm. of sodium chloride was received by those that lived and 39 gm. by those that died. The amount of sodium received also follows a somewhat similar pattern, though none of the individual comparisons between means was significantly different, statistically. Averages of 15 and 19 gm. of sodium were received in 24 hours by those who lived and those who died, respectively.

TABLE 4.—*Treatment of Diabetic Acidosis*

	Patients Who Lived				Patients Who Died				All Patients			
	3 Hr.	6 Hr.	12 Hr.	24 Hr.	3 Hr.	6 Hr.	12 Hr.	24 Hr.	3 Hr.	6 Hr.	12 Hr.	24 Hr.
Insulin, units												
Patients, no.	87	87	87	85	36	34	29	18	123	121	116	103
Mean	83	122	170	216	77	147	233	252	81	129	185	220
S. D.†	60	90	188	210	49	100	168	129	56	93	185	199
Range	0-300	0-580	0-1,630	20-1,820	0-250	0-550	0-950	140-650	0-300	0-580	0-1,630	20-1,820
Fluids, par.,† L.												
Patients, no.	87	87	87	88	35	33	29	16	122	120	116	104
Mean	1.61	2.46	3.40*	4.20*	1.72	2.95	4.46*	6.49*	1.64	2.59	3.67	4.49
S. D.	0.72	0.98	1.34	1.98	1.00	1.61	2.08	2.22	0.80	1.11	1.61	2.21
Range	0-3.0	0-5.0	0-7.0	0-8.9	0-3.5	0-6.3	0-8.0	3.0-12.0	0-3.5	0-6.3	0-8.0	0-12.0
NaCl, gm.												
Patients, no.	87	87	87	87	35	33	29	16	122	120	116	103
Mean	11.0	16.9	22.6*	27.1*	12.2	21.0	30.6*	38.7*	11.4	18.0	24.6	28.9
S. D.	6.8	8.3	11.6	14.8	7.7	12.7	16.7	22.8	7.1	9.8	13.5	16.7
Range	0-31.5	0-31.5	0-46.8	0-60.3	0-27.0	0-49.5	0-62.0	0-81.6	0-31.5	0-49.5	0-62.0	0-81.6
Sodium, gm.												
Patients, no.	87	87	87	88	35	33	29	16	122	120	116	104
Mean	6.9	10.1	13.4	15.4	7.3	11.8	16.5	19.2	7.0	10.6	14.2	16.9
S. D.	4.1	5.1	6.9	8.2	5.2	8.4	10.7	14.0	4.4	6.2	8.1	9.3
Range	0-18.2	0-24.2	0-34.7	0-38.2	0-24.5	0-40.6	0-44.9	0-51.8	0-24.5	0-40.6	0-44.9	0-51.8
Glucose, par., gm.												
Patients, no.	87	87	87	87	33	33	30	20	120	120	117	107
Mean	14.3	32.0	58.3	89.8	12.2	28.3	66.5	108.3	13.8	31.0	60.4	93.3
S. D.	30.4	42.1	66.3	88.1	23.7	43.0	84.4	108.5	28.6	42.2	71.0	91.9
Range	0-200	0-200	0-345	0-380	0-100	0-100	0-250	0-350	0-200	0-200	0-345	0-380
None, %	75.9	52.3	35.2	26.4	72.7	60.6	50.0	30.0	74.4	54.6	39.0	27.1
Mean, those given glucose	57.4	67.0	90.0	122.1	44.7	71.9	133.0	154.6	53.7	68.2	98.9	127.9
Alkali, par., gm.												
Patients, no.	....	....	....	88	....	....	....	36	....	....	....	124
Mean	....	....	....	15.9	....	....	....	16.2	....	....	....	16.0
S. D.	....	....	....	15.7	....	....	....	22.1	....	....	....	17.7
Range	....	....	....	0-44	....	....	....	0-85	....	....	....	0-85
None, %	....	....	....	37.5	....	....	....	50.0	....	....	....	41.1
Mean, those given alkali	....	....	....	25.4	....	....	....	32.4	....	....	....	27.1

* Statistically significant difference between the groups for corresponding items.
† Abbreviations are as follows: S. D., standard deviation; par., given parenterally.

Dextrose was given parenterally early in the course of treatment in only one-fourth of the cases in either group. An average of about 125 to 150 gm. was given parenterally in 24 hours (discounting patients receiving none).

Alkali given, whether as lactate or as bicarbonate, is expressed as gram equivalents of sodium bicarbonate. An average of about 16 gm. was given to the members of each group. Four-tenths of those who lived and five-tenths of those who died received no alkali. Discounting the cases in which none was given, the average amount of parenteral alkali given was 25 to 30 gm.

TABLE 5.—*Response to Treatment of Diabetic Acidosis*

	Patients Who Lived	Patients Who Died
Hr. to 1st response		
Patients, no.	87	34
Mean	3.51	....
S. D.*	6.82	....
Range	0-39	....
Immediate resp., %	60.9	....
No response, %	....	70.6
Hr. to recovery or death		
Patients, no.	84	36
Mean	21.3	21.3
S. D.	21.0	17.2
Range	0-99	5-72
Hr. to normal B. S.*		
Patients, no.	75	35
Mean	16.5	....
S. D.	20.8	....
Range	0-120	....
Normal before death, %	....	28.6
Hr. to normal CO_2*		
Patients, no.	75	35
Mean	23.5	....
S. D.	26.2	....
Range	2-170	....
Normal before death, %	....	28.6
Hr. to normal BUN*		
Patients, no.	41	18
Mean	37.5	....
S. D.	81.0	....
Range	0-408	....
Abn.* after recovery, %	7.3	....
Normal before death, %	....	11.1
Hr. to level Hb,* RBC,* or Ht.*		
Patients, no.	11	....
Mean	29.8	....
S. D.	31.4	....
Range	0-99	....
Hr. to acetone-free urin*		
Patients, no.	73	22
Mean	36.3	....
S. D.	36.6	....
Range	0-180	....
Free before death, %	....	40.9
Survival percentage	71.0	29.0

* Abbreviations are as follows: S. D., standard deviation; B. S., blood sugar; CO_2, carbon-dioxide-combining power; BUN, blood urea nitrogen; Abn., abnormal; Hb, hemoglobin; RBC, red blood cells; Ht, hematocrit reading.

Response to Treatment.—Details concerning a patient's response to therapy often go unrecorded. As a consequence such facts are difficult to extract from hospital records. The available information in the present analysis is summarized in Table 5.

An average of three and one-half hours elapsed before patients in the group that recovered first responded to questions. The longest interval was 39 hours. Sixty-one per cent of those who lived were responsive on admission. Seventy-one per cent of those who died never responded at any time.

The average elapsed time before complete recovery was 21.3 hours, and, surprisingly, for those who died the average elapsed time before death was identical. Danowski and his associates observed the same phenomenon. In their sample the average time until recovery or death was 20 hours. In the sample of adults reported by Beardwood and Rouse the average recovery time was 21.6 hours. Thus, in the typical case the issue is decided toward the end of the day of admission. However, variation from case to case is marked.

In the group of patients who lived the blood sugar returned to normal in 16.5 hours, and the CO_2 in 23.5 hours. Variation about these means was, again, quite marked. Among those who died, both these measurements were normal before death in 29%. Beardwood and Rouse noted similarly that 21% of their patients who died recovered chemically before death.

An average of 37.5 hours elapsed before azotemia disappeared among those who recovered. The longest recovery interval was 17 days. In 7% of those who recovered slight azotemia persisted. In 11% of those who died azotemia disappeared before death.

Information regarding dehydration and hemoconcentration, as represented in the hemoglobin concentration, red cell count, or hematocrit reading, was available in only 11 cases. In this meager group approximately 30 hours elapsed before hydration was relatively normal.

The urine of those who recovered became acetone-free in approximately 36 hours. In 41% of those who died acetone disappeared from the urine before death.

The over-all response of this group of patients is represented in its survival figures. Twenty-nine per cent of the 124 patients died in acidosis. The mortality percentage for any group of patients depends, of course, both on severity of the episodes and on treatment received. The mortality figures reported previously for comparable periods of data collection vary from 9 to 51%. Very probably severity of the episode is the most important determining factor in a sample like the present one, in which early therapy was not vigorous generally. However, Joslin and his associates,[4] particularly, and Harwood,[2] recently, have demonstrated the great importance of vigorous therapy in lowering mortality. The series reviewed by Dillon and Dyer was remarkably similar to the present sample in certain of its major severity characteristics (viz., age, mental state, complicating conditions, blood sugar, blood urea nitrogen, and CO_2). Perhaps one may justifiably compare their mortality rate of 36.6% with that observed in the present review.

SUMMARY

The descriptive characteristics of a representative group of patients with moderate or severe diabetic acidosis are presented in five tables under the following headings: (1) general characteristics of the patients, (2) clinical characteristics of the acidosis, (3) laboratory characteristics of the acidosis, (4) treatment received, and (5) response to treatment. Those portions of the tabulated information having greatest interest are reviewed in the text, leading to the following digested information.

Of 124 patients, 71% recovered and 29% died in acidosis. Those who died were, on the average, two decades older. They were also more obese and had higher blood pressures. More of them had no previous knowledge of their diabetes and did not take insulin, and fewer of them had previous episodes of acidosis. They were in acidosis longer before hospitalization and twice as many, proportionately, were unconscious on admission. Only two-thirds of either group had vomiting as a symptom, and very few had bloody or coffee-ground vomitus. Body temperature was lower and respiratory rate higher among those whose outcome was fatal. One-third of them were in shock on admission and three-fifths likewise at some time during the first six hours. One-half of those who died and one-tenth of those who lived had a moderate or severe complicating condition. Oliguria or anuria was present on admission in one-half of the patients who died and in one-twentieth of the surviving patients.

The degree of hyperglycemia was slightly greater among the patients who died. There was no difference between the groups in the level of the carbon-dioxide-combining power. Azotemia was much more frequent on admission among the patients who died. Two-fifths of the latter had no diacetic acid in their urine. All but a few of either group had acetonuria.

Those who lived and those who died received essentially the same treatment during the critical first three hours after admission. Thereafter the tendency was to increase slightly the vigorousness with which the more severely ill patients were treated. The patients who recovered received parenterally an average of 216 units of insulin, 4.2 liters of fluid, 27 gm. of sodium chloride, 15 gm. of sodium, 90 gm. of dextrose, and 16 gm. of alkali in 24 hours. The patients who died received parenterally an average of 252 units of insulin, 6.5 liters of fluid, 39 gm. of sodium chloride, 19 gm. of sodium, 108 gm. of dextrose, and 16 gm. of alkali in 24 hours.

The rapidity of recovery from acidosis was highly variable. An average of 21 hours elapsed before the surviving patients recovered fully. Likewise, an average of 21 hours elapsed before death occurred in the patients who died. Sixty per cent of the survivors responded to questions on admission. Seventy per cent of the patients who died failed to respond at the time of admission. In the group of patients who recovered the blood sugar returned to normal, on the average, in 17 hours, the carbon-dioxide-combining power in 24 hours, and the blood urea nitrogen in 38 hours. The urine acetone disappeared in 36 hours. The first two of these determinations were normal before death in 29% of the patients who died; the third was normal in 11%.

PROGNOSIS IN MODERATE OR SEVERE DIABETIC ACIDOSIS

Effectiveness of Various Measurements and a Derived Severity Score in Predicting the Outcome

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MINNEAPOLIS

CERTAIN measurements obtained on patients with diabetic acidosis on or shortly after admission to the hospital are known to have prognostic significance. In the past, emphasis was placed primarily on two of the measurements in determining both the existence of moderate or severe acidosis and the therapy to be given, viz., the blood sugar and carbon-dioxide-combining power. Today greater prognostic significance is attached to other criteria of severity, such as the age of the patient, the degree and duration of unconsciousness, cardiovascular and renal changes, and complicating conditions. All these important factors defining severity should of course be given careful consideration in deciding how vigorous therapy must be. No single factor is all-important, and a poor result generally follows a combination of untoward circumstances.

A quantitative evaluation of the relative prognostic significance of the important severity factors seems desirable, as does a means of combining the factors into a single weighted score which can be interpreted simply. Rabinowitch, Fowler, and Bensley [1] attempted to do this by selecting certain prognostic variables on the basis of mortality figures, rating their severity on a five-point scale to eliminate differences in units of measurement, and adding up the rating scores to get a severity index. Such an index assumed, of course, that all factors were of equal prognostic importance and did not take into account interdependence among the factors. However it forced one to give some consideration to the important severity factors and was a distinct improvement over clinical impression. On the basis of similar mortality considerations and with certain omissions and additions to the list of severity factors Collen [2] derived a similar index, which gives essentially similar information. He also constructed an arbitrary formula for predicting mortality percentage on the basis of certain graphical considerations. These indices are listed in Table 1.

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1. Rabinowitch, I. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma (An Investigation of Mortalities and Report of a Severity Index for Comparative Studies), Ann. Int. Med. **12**:1403-1428, 1939.

2. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med. **70**:347-368, 1942.

As will be shown in the following, these three severity measurements are essentially equal in value and are appreciably better than no index at all, though they are inferior to a derived combined score which takes into account quantitatively interrelationships among the severity factors. Despite their merits these indices of severity have been used very little by practicing physicians, probably because no one has demonstrated the extent and significance of their increased efficiency in predicting a good or poor result.

TABLE 1.—*Previously Recommended Indices for Combining Prognostic Factors*

Rabinowitch Index

Factor	Rating 1	2	3	4	5
Age, yr.	—15	16-30	31-50	51-70	71+
Duration of coma, hr.	—12	13-24	25-36	37-48	49+
Degree of unconsciousness	Drowsy	Semi-conscious	Uncon., reacts to pain	Completely unconscious	
Coffee ground vomitus	.....	.....	Present	.....	....
Infection	.....	.....	Present	.....	....
Blood pressure, systolic	89-80	79-70	69-60	59-50	49—
Plasma CO_2,* vol. %	19-16	15-12	11- 8	7- 4	3—
BUN,* mg./100 cc.	21-30	31-40	41-50	51-60	61+
Associated conditions	Very mild	Mild	Moderately severe	Severe	Very severe

Clinical stage	Severity Index
Very mild	0-5
Mild	6-10
Moderately severe	11-15
Severe	16-20
Very severe	21+

Collen Index

Factor	Rating 1	2	3	4	5
Age, yr.	—15	16-30	31-50	51-70	71+
Blood pressure, diastolic	69-60	59-50	49-40	39-30	—27
Complication	Very mild	Mild	Moderately severe	Severe	Very severe
Nonprotein nitrogen, mg./100 cc.	41-60	61-80	81-100	101-120	121+
Degree of unconsciousness	Drowsy	Semi-conscious	Uncon., reacts to pain	Completely unconscious	
Duration of coma, hr.	.....	.....	24+	.....	....
Blood sugar, mg./100 cc.	.....	.....	800+	.....	....

Collen Formula*

$$\text{Mort. } \% = \frac{30\,(\text{Unc.} + \text{Comp.}) + \text{Age} + 50 - \text{D. B. P.}}{4}$$

* Abbreviations are as follows: CO_2, carbon-dioxide-combining power; BUN, blood urea nitrogen; Mort. %, predicted average percentage mortality; Unc., degree of unconsciousness (graded 1 to 4); Comp., severity of complication (graded 1 to 5); D. B. P., diastolic blood pressure.

In the present study we propose to evaluate the set of measurements known or thought to be of prognostic importance in diabetic acidosis by comparing their effectiveness in differentiating between a sample of patients who lived and a sample of those who died. The best possible linear combination of the severity factors contributing to the discrimination between the groups will be derived, and the relative importance of each factor in this derived score will be evaluated. Such a formula yields a single score representing the over-all severity of the acidosis, which simultaneously takes into account every prognostic factor according to the magnitude of its contribution and thus should form the best available guide to therapy.

METHODS AND MATERIAL

Case Material.—Records of all cases of diabetic acidosis seen at the University Hospitals between 1930 and 1948 and at the Veterans Administration Hospital between 1946 and 1948 were reviewed, and detailed descriptive information was tabulated for each case as reported in the companion paper.[3] There were 124 charts containing sufficient information to enable the diagnosis of moderate or severe diabetic acidosis to be made. Of this number, 51 for patients who survived and 26 for patients who died in acidosis had complete admission data recorded for the eight variables finally considered desirable for further analysis.

Treatment received is of course important in determining the outcome of a given episode of acidosis. However, since our primary objective is to evaluate the severity measurements alone, the 26 patients who died were paired individually on the basis of treatment received with 26 of the 51 patients who lived. Table 2 summarizes the treatment characteristics of each of the final groups after the individual pairings were completed. For practical purposes the

TABLE 2.—*Comparative Treatment Received by Paired Groups*

	Patients Who Lived				Patients Who Died			
	No.*	Mean	S. D.†	Range	No.*	Mean	S. D.†	Range
Insulin, units								
3 hr.	26	90	58	0-270	26	84	53	0-250
6 hr.	26	150	111	0-580	26	155	111	0-550
12 hr.	26	242	303	0-1630	23	249	184	0-950
24 hr.	26	306	337	35-1820	12	272	147	140-650
Par.† fluids, L.								
3 hr.	25	1.65	0.70	0-3.0	26	1.60	0.94	0-3.5
6 hr.	25	2.52	0.83	0.5-3.6	26	2.94	1.62	0-6.3
12 hr.	25	3.73	1.06	1.0-5.5	24	4.52	2.20	0-8.0
24 hr.	26	5.36	2.91	1.0-8.2	11	6.12	3.05	3.0-11.7
NaCl, gm.								
3 hr.	25	12.3	6.0	0-22.5	26	11.2	7.8	0-27.0
6 hr.	24	19.0	7.2	0-27.9	26	21.1	13.7	0-49.5
12 hr.	25	27.1	11.1	0-45.0	24	30.7	17.0	0-62.0
24 hr.	25	32.4	15.1	0-60.3	12	35.6	25.9	0-81.6
Sodium, gm.								
3 hr.	25	7.4	4.1	0-14.5	26	6.7	5.2	0-24.5
6 hr.	25	11.1	4.6	0-20.7	26	11.9	9.0	0-40.6
12 hr.	26	15.6	6.0	0-24.4	24	17.1	11.3	0-44.7
24 hr.	26	17.9	7.2	0-28.8	12	19.9	15.2	3.5-51.8
Par. alkali, gm.‡								
24 hr.	25	16.5	13.3	0-50	26	15.1	23.2	0-85
Par. dextrose, gm.§								
3 hr.	25	20.0	45.6	0-200	26	11.0	24.1	0-100
6 hr.	25	42.0	52.9	0-200	26	29.6	47.0	0-150
12 hr.	25	81.6	82.1	0-345	25	65.8	88.6	0-250
24 hr.	25	131.2	96.9	0-380	15	97.7	113.4	0-350

* Any case for which there were no data recorded at a given time interval was omitted from the calculations for that interval.

† Abbreviations are as follows: S. D., standard deviation; Par., given parenterally.

‡ Parenteral alkali figures for patients that died include all cases, even though some patients died before the end of the 24-hr. period.

§ Parenteral dextrose data are inadequate for comparison purposes. For both groups approximately three-fourths of patients received no dextrose in first three hours; approximately one-half received none in first six hours.

treatment of these two groups may be considered the same. The only variables, therefore, are the prognostic (severity) measurements.

Prognostic Measurements.—Those measurements selected as worthy of detailed analysis were (1) age, (2) associated condition, (3) degree of unconsciousness, (4) duration of coma, (5) mean blood pressure, (6) blood urea nitrogen, (7) blood sugar, and (8) carbon-dioxide-combining power.

Age was recorded in years. Associated condition was rated on a six-point scale: 0, none; 1, very mild; 2, mild; 3, moderately severe; 4, severe; 5, very severe. If more than one disease state other than diabetic acidosis was present, the associated condition rating was based on the probable combined effect of the various abnormalities. Any infection that was present

3. Zieve, L., and Hill, E.: Descriptive Characteristics of Group of Patients with Moderate or Severe Diabetic Acidosis: Relation to Recovery or Death, A. M. A. Arch. Int. Med., this issue, p. 51.

was considered an associated condition and was rated similarly. Degree of unconsciousness was rated on a five-point scale: 0, conscious and alert; 1, drowsy; 2, semiconscious; 3, unconscious but responding to pain; 4, unconscious and unresponsive. Duration of coma was measured in hours. The word "coma" is used in a generic sense, to include all degrees of cerebral depression from drowsiness and semiconsciousness to complete unconsciousness. Absence of coma is represented by a duration of zero hours. The exact point at which the patient's decreased sensibility began was estimated on the basis of symptoms elicited and relatives' descriptions of the patient's behavior. The estimates are at best approximate.

The mean blood pressure, i. e., (systolic + diastolic)/2, was selected in preference to either systolic or diastolic pressure alone. It reflects changes in both. No attempt was made to take into account previously existing hypertension, since we have no means of equating a drop in blood pressure at hypertensive levels to one at normotensive levels.

Determination of blood urea nitrogen, like all the other measurements, was obtained on or very shortly after admission. Other available measures of renal status of differential significance were presence of oliguria or anuria and absence of diacetic acid from the urine. The blood urea nitrogen level adequately reflects these changes. Blood sugar and carbon-dioxide-combining-power values used were the admission values.

TABLE 3.—*Summary Data for Eight Prognostic Factors and the Derived Severity Score, by Group*

Variable	Patients Who Lived (No. = 26)			Patients Who Died (No. = 26)		
	Mean	S. D.*	Range	Mean	S. D.*	Range
Age, yr.	31.5	15.9	13-63	53.5	17.6	18-77
Associated condition, deviation units	+0.47	0.76	−1.22-+1.10	−0.47	0.90	−2.00-+1.10
Degree of unconsciousness, deviation units	+0.40	1.06	−1.61-+1.77	−0.40	0.66	−1.61-+0.86
Duration of coma, hr.	2.4	3.9	0-12	10.4	12.1	0-48
Mean blood pressure, mm. Hg	104	17.6	68-162	73	31.4	0-125
BUN,* mg./100 cc.	24	13.3	7-55	44	22.3	12-109
Blood sugar, mg./100 cc.	543	249	204-1076	617	236	335-1165
CO_2,* vol. %	21.0	7.8	11-37	19.7	9.2	9-40
Severity score, units	+24.0	24.2	−31.5-+88.6	−24.0	21.5	−62.2-+18.6

* Abbreviations are as follows: S. D., standard deviation; BUN, blood urea nitrogen; CO_2, carbon-dioxide-combining power.

Detailed review of the other data recorded in the companion paper revealed no additional factors that seemed desirable to include in an extensive analysis beyond these eight initially selected on the basis of previously published studies.[4] The raw data for each person in each of the two groups are summarized in Table 3. In all computational procedures with the data six decimal places have been carried throughout. Figures have been rounded off only in the final stage after completion of calculations or for purposes of tabulation.

Conversion of Qualitative Ratings to Quantitative Form.—Two measurements, associated condition and degree of unconsciousness, are qualitative (ratings) in form and yet are of such basic importance in any analysis of severity of diabetic acidosis that they cannot be overlooked. In order that these variables might be utilized in further calculations, they were converted to quantitative form by alignment of the ratings with the normal distribution curve, as described by Kelley.[5] A low rating is represented by a deviation in the positive direction and a high rating by a deviation in the negative direction. Therefore the direction of abnormality is indicated by an algebraically decreasing score. Associated condition and degree of unconsciousness are similar in this respect to blood pressure and carbon-dioxide-combining power.

4. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, Ed. 8, Philadelphia, Lea & Febiger, 1946, p. 448. Dillon, E. S., and Dyer, W. W.: Factors Influencing Prognosis in Diabetic Coma, Ann. Int. Med. **11**:602-617, 1937. Rabinowitch.[1] Collen.[2]

5. Kelley, T. L.: Statistical Method, New York, The Macmillan Company, 1923, p. 101.

Combination and Comparison of Prognostic Factors.—Details of the statistical procedure for combining a set of variables linearly in optimal fashion for purposes of discriminating between two groups have been presented elsewhere.[6] In essence, for the present application, a set of weights (or coefficients) corresponding to the set of prognostic factors is derived, the significance of the weights is determined, and those factors having insignificant weights are eliminated. The remaining independently significant factors are multiplied by their respective weights and added together to form a single score, which is then compared with the corresponding score resulting from combination of all the original factors. An insignificant difference between the discriminative powers of these scores indicates that little is lost by omitting the factors with insignificant weights.

The score derived from the independently significant factors represents the best possible combination (linear) of the available information for purposes of differentiating patients who are likely to die from patients who are likely to live, other things being equal. The relative effectiveness of this score in comparison with the separate factors or derived indices of Rabinowitch and his associates and Collen, or of the separate factors in comparison with each other, is determined from an analysis of variance, in which a "discrimination ratio" and a *t* value (representing the significance of differences between means) are calculated. The discrimination ratio for any given measure is that fraction of the total variation among the

TABLE 4.—*Discriminative Effectiveness of the Individual Prognostic Factors*

Factor*	Discrimination Ratio (× 100), %†	*t*
Age	31.1	4.7
BP	28.1	4.4
AC	24.4	4.0
BUN	22.8	3.8
DU	17.8	3.3
DC	16.9	3.2
BS	2.4	1.1
CO_2	0.6	0.5

* Abbreviations are as follows: BP, blood pressure; AC, associated condition; BUN, blood urea nitrogen; DU, degree of unconsciousness; DC, duration of coma; BS, blood sugar; CO_2, carbon-dioxide-combining power.

† Discrimination Ratio = fraction of total variation among persons of both groups that is due to average differences between the groups.

individuals of both groups that is attributable to average differences between the groups. A ratio of 0.75 (or 75%, if taken times 100) represents nearly complete separation of the groups, with relatively little overlapping.

RESULTS AND INTERPRETATIONS

Discriminative Power of the Prognostic Variables Considered Individually.—The data of each factor listed in Table 3 were subjected to an analysis of variance. The discrimination ratios and *t* values resulting from this analysis are listed in Table 4.

All the variables differentiate significantly between the group of patients who lived and those who died, with the exception of the blood sugar and carbon-dioxide-combining power. The most significant single factor, considered separately, is the age of the patient. Of the total variation in age 31.1% is due to average differences between those who lived and those who died. The difference between means is 4.7 times its standard error. The degree of separation of the two groups by the other factors decreases progressively, though all, except blood sugar and carbon-dioxide-combining power, are significant.

6. Zieve, L.: Thesis, University of Minnesota, Appendix IIB, 1952.

The significant severity factors may be grouped into three levels according to their effectiveness in separating the two groups: highest, age and mean blood pressure; intermediate, associated condition and blood urea nitrogen; lowest, degree of unconsciousness and duration of coma.

The difference between means for the blood sugar, 74 mg. per 100 cc., is insignificant. In the parent samples from which the cases considered in this paper were drawn the difference between means (110 mg. per 100 cc.) was significant.[3] However, in that instance there was no selection of cases for control of treatment variables.

Derived Weights and Formula for Combining the Prognostic Factors into a Single Severity Score.—The initial weighting factors for the prognostic variables were derived by solving a set of eight equations (involving as coefficients the product sums and sums of squares within groups and as constant terms the differences between the means of each group). In the process of solving these equations the interdependence of the original measurements is taken into account, and the final weight for any given one represents the contribution of that measure independent of all the others. All the factors except age, degree of unconsciousness, and carbon-dioxide-combining power had significant weights. Tests of significance of the weights of the latter three factors yielded the following insignificant t values, respectively: 0.30, 1.62, and 1.58.

Age, which had the greatest differential value when considered alone, has no contribution to the severity score that is independent of the other factors. Its previous differential value reflected merely its association with cardiorenal status and abnormalities of electrolyte metabolism. The lack of significance of degree of unconsciousness most likely reflects the crude nature of the procedure for conversion from qualitative to quantitative form. Extraneous errors, such as that introduced by representing a broad category by a single score, tend to reduce its discriminative power. Carbon-dioxide-combining power had little differential value either before or after taking into account its correlation with other variables. The over-all discriminative power of the formula formed by combining all the prognostic factors, including the three with insignificant weights is indicated by its discrimination ratio of 74.7%.

Having insignificant weights, age and carbon-dioxide-combining power were eliminated from the formula and the coefficients of all the other variables readjusted appropriately. Degree of unconsciousness was retained in anticipation of a possibly significant weighting factor upon elimination of the other two variables. The final weighting factors corresponding to each variable remaining, along with the standard errors of the weights and the results of testing whether or not they deviate significantly from zero, are listed in Table 5.

The signs attached to the weights reflect the combined effect of the direction in which abnormality is measured and of the sign attached to the difference between means (i. e., whether we compare those who lived with those who died, as was done, or those who died with those who lived). Thus duration of coma and blood urea nitrogen, whose directions of abnormality are represented by increasing values, have weights with negative signs attached, and associated condition, degree of unconsciousness, and blood pressure, whose directions of abnormality are represented by decreasing values, have weights with positive signs attached. The sign

of the weighting factor for blood sugar is contrary to that expected since its direction of abnormality is similar to that of duration of coma.

All the factors are highly significant as before, except for degree of unconsciousness, which has just become significant at the 5% level. As seen from the t values, the order of effectiveness of the severity factors, now that their interdependence has been taken into account, is different from that found on separate analysis of each factor. Associated condition, blood urea nitrogen, and blood sugar are most effective; duration of coma and blood pressure intermediate in effectiveness, and degree of unconsciousness least effective.

The blood sugar factor found to be highly significant in the formula is not the same as the actual blood sugar determination previously found to be insignificant. The latter is the net result of various factors operating in the body, including certain of the other prognostic variables we have measured. If we take into account the way these other factors correlate with the blood sugar and eliminate their influence, as was done in the formula, we can derive new values which are independent of them. The direction of abnormality of these derived values is opposite

TABLE 5.—*Final Weighting Factors and Their Tests of Significance*

	Final Weighting Factor	SE* of Final Weighting Factor	t	Proportional Form of Final Weighting Factor
AC*	0.060261	0.015044	4.01	—13.88
DU	0.029309	0.014971	1.96	—6.75
DC	—0.004341	0.001411	3.08	1.00
BP	0.001454	0.000478	3.05	—0.33
BUN	—0.004135	0.001115	3.71	0.95
BS	0.000422	0.000112	3.77	—0.10

* Abbreviations are as follows: SE, standard error; AC, associated condition; DU, degree of unconsciousness; DC, duration of coma; BP, blood pressure; BUN, blood urea nitrogen; BS, blood sugar.

to that of the actually determined values, since the sign of the weighting factor is positive instead of negative as expected. Therefore increasingly abnormal observed blood sugar values indicate decreasingly abnormal derived values which have prognostic significance. In terms of prognosis for a given degree of severity a high blood sugar is thus a good omen and a low blood sugar an ill omen in diabetic acidosis.

Differentiation of the groups by the revised formula is highly significant, as was to be expected. Of the total variation, 73.1% is due to average differences between the two groups, indicating again excellent separation of the groups. Eliminating age and CO_2-combining power had very little effect on the discriminative value of the combined severity score, as evidenced by the insignificant decrease of 1.6% in the discrimination ratio ($F = 1.39$, $P > 0.2$).

In actual use the weighting factors are converted to proportional form, i. e., all are divided through by one of them. They are listed in this form in the last column of Table 5. Utilizing these coefficients, the best possible linear formula combining the severity factors may be written

$$X = -13.88\,AC - 6.75\,DU + DC - 0.33\,BP + 0.95\,BUN - 0.10\,BS.$$

Simplified Form of the Formula.—Without changing anything significantly the calculation and use of the severity score may be simplified by rounding off the

coefficients, multiplying through by —1, subtracting a constant so that a zero value will be half way between the means for the groups of those who lived and those who died, and rearranging terms. The severity score (SS) formula then becomes SS = (14 AC + 7 DU) + (0.3 BP + 0.1 BS) — (DC + BUN + 44).

Zero is the dividing line between those who generally die (negative score) and those who generally live (positive score). The scores obtained with this formula are summarized in Table 3. Of those who lived, only one had an appreciably negative severity score, and of those who died only two had an appreciably positive score. There is thus nearly complete separation of the two groups. From the formula it is again evident that a high blood sugar is a favorable sign.

Comparative Discriminative Efficiency of the Severity Score and Other Prognostic Measurements.—Table 6 lists the various prognostic factors and derived combinations of these factors, arranged in order of discriminative effectiveness. The prognostic variables individually considered are far less effective than

TABLE 6.—*Comparative Discriminative Effectiveness of the Severity Score and Other Prognostic Measurements*

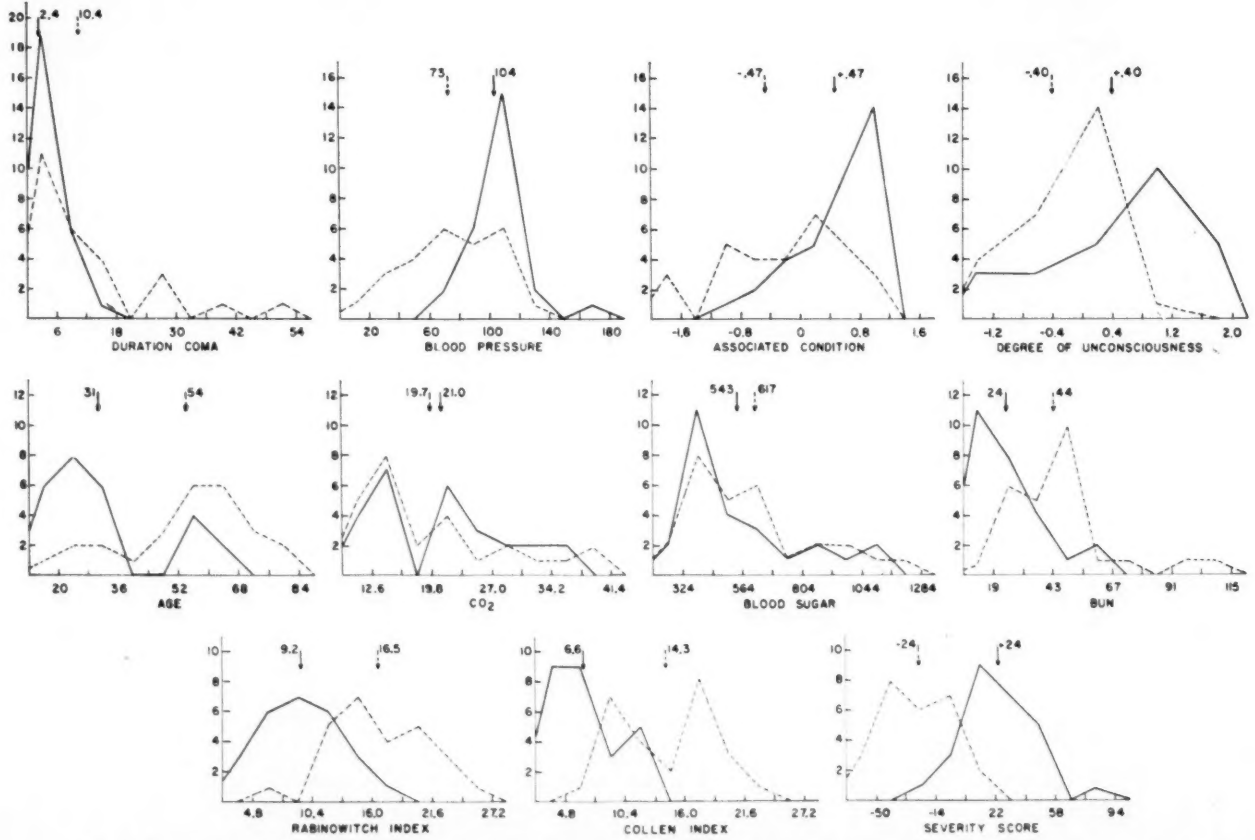
Factor*	Discrimination Ratio (× 100)	
	Observed, %	Relative
Severity score	73.1	1.00
Collen index	51.1	0.70
Rabinowitch index	45.9	0.63
Age	31.1	0.43
BP	28.1	0.38
AC	24.4	0.33
BUN	22.8	0.31
DU	17.8	0.24
DC	16.9	0.23
BS	2.4	0.03
CO_2	0.6	0.01

* Abbreviations are as follows: BP, blood pressure; AC, associated condition; BUN, blood urea nitrogen; DU, degree of unconsciousness; DC, degree of coma; BS, blood sugar; CO_2, carbon-dioxide-combining power.

any of the combinations. The simple procedures utilized by Rabinowitch and his associates and Collen appreciably improved the discrimination between patients who are apt to die and those who are likely to survive, but they did not approximate the effectiveness of the severity score. With the latter, the difference between the means of the groups is 73.1% of the total variation observed (and is 11.1 times its standard error). The simpler combinations of Rabinowitch and Collen are approximately two-thirds as effective, and the significant prognostic factors, considered separately, are approximately one-third as effective. The degree of separation of the two groups by each of these measurements is portrayed graphically in the chart.

One may obtain additional comparative information of a different sort from the correlations, within groups, between the severity score and the other prognostic measurements. Fisher [7] has shown that any measurement may be rejected as less effective than such a linear function if its correlation with it, within groups, is less than a certain value determined from a significance test. In the present instance it

7. Fisher, R. A.: The Precision of Discriminant Functions, Ann. Eugenics **10**:422-429, 1940.



Frequency distributions of prognostic factors and derived scores. The solid line indicates patients who lived; the broken line, patients who died; the ordinates, number of patients; arrows and numbers at the top of graphs, mean values.

is unlikely (probability 0.05) that a correlation less than 0.84 between the severity score and any equally discriminating linear measure would occur by chance. Therefore any measure whose correlation with the severity score is 0.84 or better may be considered as effective as this score, and any measure whose correlation is less than 0.84 is significantly less effective.

The severity score, calculated from the simplified form of the final formula, correlates nearly perfectly with the exact formulas utilizing the six independently significant factors or all eight factors ($r = -0.999$ and -0.982, respectively). This shows again, incidentally, that little is lost by dropping age and CO_2-combining power from the formula. The correlation of the severity score with blood

TABLE 7.—*Summary of Information Needed to Calculate Severity Score*

Severity score = I + II − III

I = (14 AC + 7 DU)	AC = Associated Condition
	DU = Degree of Unconsciousness
II = (0.3 BP + 0.1 BS)	BP = Mean Blood Pressure (S + D)/2
	BS = Blood Sugar, mg./100 cc.
III = (DC + BUN + 44)	DC = Duration of Coma, hr.
	BUN = Blood Urea Nitrogen, mg./100 cc.

Zero is the dividing line between those who generally die (negative score) and those who generally live (positive score).

The quantitative value of Term I is obtained directly from the table below.

Rating of DU	Rating of AC: 0	1	2	3	4	5
0	27.9	14.5	7.6	2.0	−4.6	−15.6
1	21.4	8.1	1.1	−4.4	−11.0	−22.0
2	15.6	2.2	−4.7	−10.2	−16.9	−27.9
3	10.2	−3.2	−10.1	−15.6	−22.3	−33.3
4	4.2	−9.2	−16.1	−21.6	−28.3	−39.3

Rating scheme of AC
0 None
1 Very mild
2 Mild
3 Moderately severe
4 Severe
5 Very severe

Rating scheme of DU
0 Conscious and alert
1 Drowsy
2 Semiconscious
3 Unc. but responds to pain
4 Unc. and unresponsive

pressure, which may be taken to represent any one of the more effective single factors, is only 0.25. Similarly the correlations of the severity score with the Rabinowitch index, the Collen index, and the Collen formula are −0.39, −0.31, and −0.39, respectively. The signs of the correlations indicate merely the relative directions of abnormality of the variables. Thus none of the prognostic factors nor any of the previously suggested methods for combining the factors approximates the effectiveness of the severity score in distinguishing between patients who live and patients who die.

Practical Use of the Severity Score Formula.—The clinical use of the formula is very simple. The information required is summarized in Table 7. Since associated condition and degree of unconsciousness must be in quantitative form in the formula and are utilized clinically as qualitative ratings, the calculation has been simplified by constructing a table which enables the value of Term I to be obtained directly from the ratings of associated condition and degree of unconsciousness.

We may illustrate the computational procedure with two clinically obvious examples. Example 1: Given AC = 2, DU = 4, BP = 58/34, BS = 800, DC = 30, BUN = 90. From the third column and fifth row of the table in Table 7, get value of —16.1 for the quantity (14 AC + 7 DU), which is Term I in the formula. Calculate $0.3 \times (58 + 34)/2 + 0.1 \times 800$, which gives 93.8 for Term II. Add 30 + 90 + 44 to get 164 for Term III. Combine these values for each term according to the formula, —16.1 + 93.8 —164, giving —86.3 as the severity score.

Example 2: Given AC = 0, DU = 1, BP = 120/80, BS = 500, DC = 3, BUN = 20. The value for Term I is 21.4, taken directly from Table 7. Term II is $(0.3 \times 100) + (0.1 \times 500) = 80$. Term III is 3 + 20 + 44 = 67. Substituting for each term gives 21.4 + 80 —67 = 34.4, the severity score.

Two precautions should be noted. The formula is no better than the data on which it is based. If erroneous clinical estimates are made or if large technical errors are present in laboratory results, the resulting severity score will be erroneous. The severity score, like all empirical formulas, is invalid outside the range of its derivation. If it is applied to a normal person, the result is meaningless. An error of diagnosis will result, of course, in an erroneous severity score.

Clinical Implications of the Severity Score.—It is apparent from the foregoing analysis that a weighted combination of the significant prognostic factors yields much more information than mere examination of the individual factors and is correspondingly more useful clinically. The severity score forces us to recognize all the factors of importance in determining the outcome of the acidosis at the time we first see the patient. Neglect of any one factor is less likely. In addition, a single score indicating the status of the patient comprehensively should be valuable in guiding therapy.

Recognition of other prognostic factors of significance which were not taken into account here does not detract from the usefulness of the score as derived. Addition of any new factors at some future date, should such data become available, will add to the discriminative efficiency of the formula without negating its present value. Data on the serum potassium concentration, which has received a great deal of attention in recent years, were unavailable; so its prognostic significance could not be evaluated. It should be noted, however, that alterations in serum potassium of known prognostic import occur generally in the six- to twelve-hour period after therapy has been started and not at the time of admission to the doctor's care.

SUMMARY

Factors of prognostic importance in moderate or severe diabetic acidosis have been evaluated with respect to their effectiveness in discriminating between patients who survive and patients who die of acidosis. The independently significant factors have been combined in a weighted formula yielding a single score representing the over-all severity of the acidosis with optimal effectiveness.

Considered individually, the order of effectiveness of the significant prognostic variables was age, blood pressure, associated condition, blood urea nitrogen, degree of unconsciousness, and duration of coma. Blood sugar and carbon-dioxide-combining power did not significantly differentiate between the two groups.

When considered simultaneously, with allowances for their interdependence, the measurements may be regrouped into three levels of significance, as follows: highest, associated condition, blood sugar, and blood urea nitrogen; intermediate, blood pressure and duration of coma, and lowest, degree of unconsciousness. Age had no independent contribution, and carbon-dioxide-combining power remained insignificant. For a given degree of severity, a high blood sugar was observed to be a favorable prognostic sign.

The severity score, representing an optimal linear combination of the independently significant variables, was three times as effective as the prognostic factors considered individually and one and one-half times as effective as any of the previously suggested methods for combining the factors.

A simplified tabulation is presented enabling ready application of the formula in practice.

SHOCK-LIKE STATE DUE TO TRANSFUSION OF BLOOD CONTAMINATED WITH GRAM-NEGATIVE BACILLI

Successful Treatment with Antibiotics and Arterenol

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WHEN GREAT numbers of certain gram-negative bacilli enter the circulating blood their endotoxin produces hypotension. If the amount or potency of endotoxin is not too great, the hypotension is only moderate and temporary. Treatment with extracts of Pseudomonas aeruginosa in essential hypertension is based on the mild hypotensive effects of endotoxin which has been carefully standardized for clinical use.[1] Under other conditions endotoxin in the circulating blood may produce an irreversible and severe hypotension leading to a fatal shock-like state.

One of the most dramatic causes of this shock-like state is transfusion of blood contaminated by bacteria. Borden and Hall [2] have recently presented an excellent account of the syndrome arising from the transfusion of contaminated blood. They reported two fatal cases and reviewed the eight additional cases in the literature. The reactions in these cases were all characterized by the transfusion of blood containing Gram-negative bacilli, by peripheral vascular collapse, and, with one exception, by a fatal outcome. The case in which the patient recovered was made known to Borden and Hall in a personal communication from Whitby, and the details of therapy are not generally available.

Recently a severe transfusion reaction due to massive bacterial contamination of banked blood was observed on the wards of the University of Michigan Hospital. Recovery from the bacteremia and state of shock was brought about by several agents. Their successful use in this case is reported to encourage their trial in other patients suffering from bacteremic shock.

From the Department of Internal Medicine, University of Michigan Medical School. The bacteriologic studies were supported in part by a grant from the Medical Research and Development Board, Office of the Surgeon General, Department of the Army.

1. Page, I. H., and Taylor, R. D.: Pyrogens in the Treatment of Malignant Hypertension, Mod. Concepts Cardiovas. Dis. **18**:51, 1949.

2. Borden, C. W., and Hall, W. H.: Fatal Transfusion Reactions from Massive Bacterial Contamination of Blood, New England J. Med. **245**:760, 1951.

REPORT OF A CASE

The patient was a 28-year-old war veteran who had served in the Asiatic theater. He entered the University of Michigan Hospital on Sept. 13, 1952, complaining of recurrent attacks of chills, sweats, and fever and of marked weight loss and weakness. The symptoms had been present for four months. The attacks of fever were remarkably periodic, in that they returned every two weeks. The duration of each period of fever was one week. Blood cultures obtained after the patient entered the hospital were sterile. A cervical lymph node was removed, and microscopic examination disclosed changes typical of Hodgkin's disease. The patient was treated with x-ray for 13 days and improved, with apparent cessation of fever. He remained anemic, however, and two blood transfusions were given. The first 500 cc. of blood was transfused on Sept. 25, 1952, with no difficulty. On Sept. 26, 1952, a second transfusion of blood was started at 8:50 a. m. Before 50 cc. of blood had left the bottle, the patient began to experience shaking chills, severe cramplike abdominal pain, nausea, and vomiting. The transfusion was stopped at 9:30 a. m., but the chills continued and the temperature rose from 98.6 to 102 F. by 10:30 a. m. and to 104 F. by 12 noon.

Blood was drawn for evidence of hemolysis, and none was found. No urine was passed for examination. A direct smear of the blood in the bottle used for the transfusion was made less than one hour after the reaction occurred. Numerous Gram-negative bacilli were observed in each microscopic field. No incompatibilities of blood type were detected. The demonstration of Gram-negative bacilli in the smear of blood led to a diagnosis of massive bacterial transfusion reaction, and this was supported clinically by the development of severe hypotension. Less than three hours after the reaction, the blood pressure had dropped from the normal 120/70 to 86/70. The patient suffered from severe nausea, vomiting, diarrhea, sweats, cyanosis, flushing, and abdominal pain during the next 12 hours. His sensorium was perfectly clear, however, and his general appearance did not at first suggest his perilous condition.

At 4:00 p. m. a blood culture was taken, and then antibiotics were given. Because the identity of the Gram-Negative bacilli was unknown, several different antibiotics were administered. First, 500 mg. of aureomycin was injected intravenously at 4:00 p. m., as a means of treating a bacteremia due to coliform bacilli. To cover the possibility of an infection by Ps. aeruginosa, the patient received 100 mg. of polymyxin B (Aerosporin) at 8:45 p. m., 11:45 p. m., 2:45 a. m., and 5:00 a. m. A combination of penicillin procaine and chloramphenicol was used to cover Proteus organisms. An intramuscular injection of 1,000,000 units of penicillin procaine and 0.5 gm. of chloramphenicol orally was given at midnight. The dose of chloramphenicol was repeated six hours later.

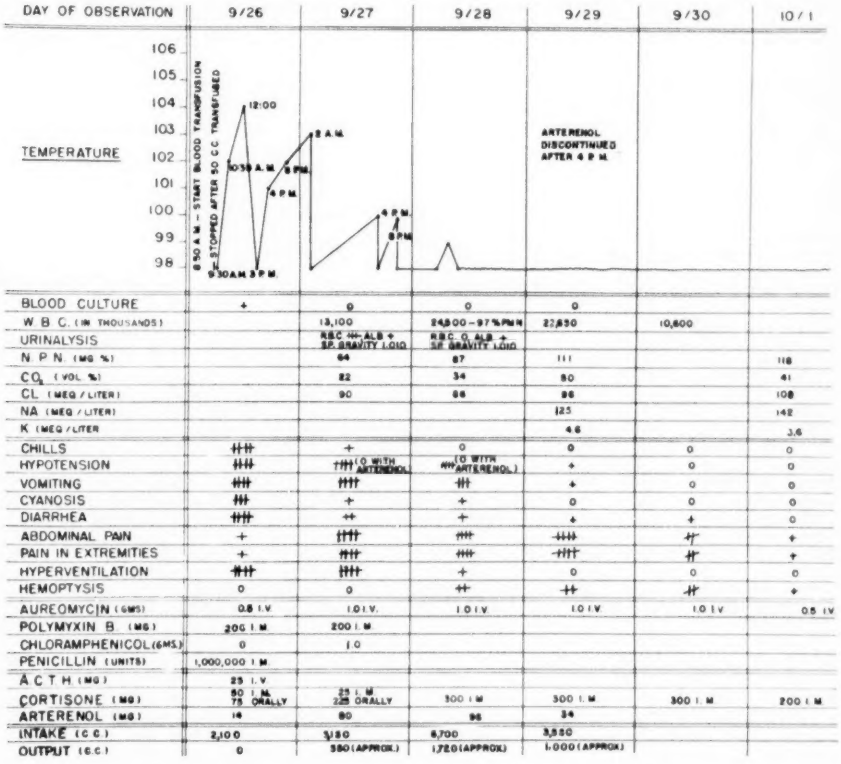
Arterenol (Nor-epinephrine) was used to correct the hypotension, beginning at 5:00 p. m. on the day of the reaction. This agent was given in the form of an intravenous drip in water containing 5% dextrose. The patient required 14 mg. of arterenol during the first 6 hours, 80 mg. on the second day, 96 mg. on the third day, and 34 mg. during the final 16 hours. Then it was found possible to discontinue its use. An intravenous drip of 40 to 50 drops per minute of a solution containing as much as 24 mg. per liter was required to maintain the blood pressure at 100/70. Precipitous falls in pressure resulted when the arterenol was stopped even momentarily.

Corticotropin (ACTH) and cortisone were also given to treat shock. A dose of 25 mg. of corticotropin in a liter of 5% dextrose was given intravenously from 5:00 p. m. to 11:00 p. m. on Sept. 26, 1952, for its immediate stimulating effect on the adrenals. During the first 24 hours the patient also received 300 mg. of cortisone orally and 50 mg. intramuscularly in divided doses. Thereafter he was treated with cortisone given intramuscularly in doses of 75 mg. every six hours.

The effects of treatment with antibiotics, arterenol, steroids, and fluids were immediately apparent. After a second rise in fever, to 103 F., during the early morning of Sept. 27, the temperature returned to normal and did not rise again above 100 F. during the remainder of treatment. Cultures of the patient's blood before treatment, taken at 4:00 p. m. on Sept. 26, yielded so many Gram-negative bacilli per milliliter that they could not be counted in the poured plate. This bacillus was subsequently identified as an intermediate type of coliform bacillus. By the morning of Sept. 27, 14 hours after the start of treatment with antibiotics, the blood

had become sterile. At that time the results were known of sensitivities to antibiotics of the two species of bacilli grown from the bottle of contaminated blood. These two species of organisms were later identified as Escherichia freundii and a coliform bacterium of intermediate type. These were both very sensitive to aureomycin, and the patient was subsequently treated by the daily administration of 1 gm. of aureomycin intravenously.

When the blood pressure was kept at normal levels with arterenol, the patient's sensorium was clear. When use of arterenol was stopped, the pressure fell abruptly to 60/30 or less and confusion, labored respirations, and apprehension were manifested. His chief complaint at all times was pain and stiffness. There was severe abdominal pain aggravated by vomiting and



Treatment of bacteremic shock resulting from transfusion of 50 cc. of blood massively contaminated with Escherichia freundii and a coliform bacillus of intermediate type.

related to protracted diarrhea. He also suffered from marked tenderness of the skin and muscles of the entire trunk and extremities, and he resisted nursing care which involved handling. Severe nausea in the presence of food existed for several days.

During the first 24 hours, there was complete anuria associated with rapid development of uremia and acidosis. On the morning of Sept. 27 the blood nonprotein nitrogen was 64 mg. per 100 cc., the chlorides 90 mEq. per liter, and the CO_2 22 vol. %. Shortly after these determinations were made, at 11:00 a. m. on Sept. 27, the patient passed 150 cc. of cloudy, brown, acid urine loaded with erythrocytes. The specific gravity was 1.010. On Sept. 27 he received 1,150 cc. of isotonic sodium chloride solution, 300 cc. of $NaHCO_3$, and 3,700 cc. of dextrose in water. Much of this fluid was required as a vehicle for administering the arterenol. He was also given a tranfusion with 500 cc. of blood.

On Sept. 28 he received the massive dose of 96 mg. of arterenol and his general condition remained fairly good. He urinated 2,400 cc., and the hematuria gradually disappeared. The urine then contained only 1 + albumin and no casts, but the specific gravity remained at 1.010. The nonprotein nitrogen at 9:00 a. m. on Sept. 28 was 87 mg. per 100 cc., the CO_2 was 34 vol. %, and the chlorides were 86 mEq. per liter. Parenteral fluids on that day consisted of 2.7 liters of isotonic sodium chloride, 2 liters of ⅙ molar lactate solution, and a liter of 10% dextrose in water. By gradually reducing the concentration of arterenol to 8 mg. per liter, on Sept. 29, it was possible finally to discontinue its use permanently at 4:00 p. m. on that day. At first the blood pressure was 80/60, but after several hours it gradually rose to 100/70, and by Oct. 3 it had risen to 120/80, where it remained. The only noticeable harm from arterenol was inflammation of the right antecubital vein, where the drug was injected by drip during the first few days. Warm moist packs relieved the phlebitis.

TABLE 1.—*Comparison of Biologic Properties of Gram-Negative Bacilli Cultured from Bottle of Transfused Blood and from Patient's Blood after Transfusion Reaction*

	Origin of Bacillus		
	Transfused Blood	Transfused Blood	Patient's Blood
Gram's stain	Short, fat, Gram-negative rods	Short, fat, Gram-negative rods	Short, fat, Gram-negative rods
Motility	+	+	+
Russell's double sugar medium	A/AG *	A/AG	A/AG
Citrate (Simmon's) medium	+	−	−
Methyl red	+	−	−
Urea	−	−	−
Lactose (fermentation)	AG	AG	AG
Dextrose (fermentation)	AG	AG	AG
Glycerin	Slight AG	Slight AG	AG
Indole	Slight +	−	−
Voges-Proskauer reaction	−	+	+
Nitrites	−	±	+
H_2S	+ 24 hours	+ 48 hours	−
Catalase	+	+	+
Gelatin (liquefaction)	−	+ 48 hours	+ 48 hours
Litmus milk	Acid in 48 hours, coagulated	Acid in 48 hours, coagulated	Acid in 48 hours, coagulated
Pigment production	−	−	−
Eosin methylthionine chloride agar	37 C., slight growth, purple; 4 C., slight pink growth, 4 days	37 C., scant growth, purple; 4 C., slight colorless growth, 4 days	37 C., scant growth, purple; 4 C., slight colorless growth, 4 days
Identification	Escherichia freundii	Coliform bacillus of intermediate type	Coliform bacillus of intermediate type

* A indicates acid; G, gas.

Despite general improvement, good urinary output, and weaning from arterenol, nitrogen retention increased. By Oct. 1 the nonprotein nitrogen had reached 118 mg. per 100 cc., although the chloride, CO_2, sodium, and potassium levels were normal. The serum phosphorus at this time was 7.2 and the calcium 7.4 mg. per 100 cc. After Oct. 1 the nonprotein nitrogen gradually fell and in five days had nearly returned to normal. On Oct. 6 the urinalysis showed no abnormalities and the specific gravity was 1.015.

As a result of treatment with fluids and cortisone the patient gained 20 lb. (9 kg.). The dose of cortisone was gradually reduced, starting on Oct. 1, and was discontinued on Oct. 4. Most of the weight due to accumulation of water was lost. During treatment for the transfusion reaction hemoptysis and a consolidation of the right lower lobe also developed. This complication was probably due to aspiration of vomitus and later subsided.

After cortisone was discontinued the patient was weak but otherwise appeared to convalesce satisfactorily. On Oct. 11 there was a return of Pel-Ebstein fever. The patient was discharged from the hospital on Oct. 16, despite the fever, to await full effects of treatment by irradiation. Three weeks later he entered the hospital again. The severity of Hodgkin's disease progressed and led to his death, on Dec. 5, 1952, but the septicemia, or shock-like state, never returned.

BACTERIOLOGIC STUDIES

Two species of bacteria were isolated from the bottle of transfused blood. One of these gave the typical reactions of E. freundii. The other fermented lactose actively to acid and gas and gave a typical reaction for the coli-aerogenes group on Russell's double sugar medium. The second organism, therefore, belongs to the coliform group and resembles Aerobacter aerogenes somewhat by forming acetylmethylcarbinol in the Voges-Proskauer test. It cannot be identified as A. aerogenes, because of its inability to utilize citrate on Simmon's medium. Instead it is classified as a coliform bacillus of intermediate type. A total of 3×10^9 bacilli were counted in 1 ml. of the contaminated blood, using poured plates made with appropriate serial dilutions.

The biologic properties of the bacillus isolated from the patient's own blood after the transfusion reaction were identical in many ways to those of the coliform bacillus of intermediate type present in the donor's contaminated blood. These

TABLE 2.—*Rate of Growth of Bacteria Inoculated into Citrated Blood and Stored in Refrigerator (4 C.) and at Room Temperature (27 C.)* *

Bacteria	Temperature of Storage, C.	Number of Viable Bacteria/Ml. Stored Blood — Duration of Storage, Hr. 0	6	24	72	168 (1 Wk.)
Coliform bacillus of intermediate type	4	26	22	22	20	9
		5,400	1,590	630	347	681
	27	51	42	73	30	2
		6,040	30	430,000,000	..	..
Escherichia freundii	4	25	26	22	19	7
		14,340	21,150	56,000	16,800	..
	27	37	69	33	45	3
		15,720	310	360,000,000	..	..

* These bacteria had been originally isolated from the contaminated bottle of transfused blood. They were subsequently inoculated in the laboratory into blood donated by the original donor for purposes of this experiment.

reactions are summarized in Table 1. All three bacilli were also examined for growth at 4 C. The coliform bacillus isolated from the patient's blood produced visible growth on blood agar and in tryptose broth in three days and was not hemolytic at that temperature on blood agar. The coliform bacillus isolated from the bottle of contaminated blood grew visibly with slight hemolysis on blood agar but not until the 10 days, and in broth not until the 14 days at 4 C. E. freundii isolated from the bottle first produced visible growth in broth and on blood agar with slight hemolysis on the 14th day. Small inoculums of each of the three bacilli grew heavily in broth and on blood agar at 37 C. and 27 C. within 24 hours.

The transfused blood was stored at 4 C. for eight days before the day of the reaction. Contaminants were introduced sometime during that period, probably when blood was removed from the bottle for the Kahn test. As the donor was employed by the University of Michigan, additional blood was available from her for studies of its activity against the contaminants at 4 C. and at room temperature, under conditions comparable to those existing during storage of the banked blood. The results are shown in Table 2. They disclose that no significant growth occurred at 4 C. with either large or small inoculums. At 27 C. no growth occurred with small inoculums in one week and with large inoculums the number of viable bacteria of either strain was greatly reduced in six hours. By 24 hours, however, both

the coliform bacteria and the E. freundii had reached tremendous numbers at room temperature.

Studies relating to hemolytic activity are summarized in Table 3. The two coliform bacteria were hemolytic at 37 C. both on blood agar and when inoculated into tubes of human blood. The coliform bacteria obtained originally from the contaminated bottle of blood, however, had decidedly more hemolytic activity in whole blood at 37 C. and, of the three organisms tested, was the only one which hemolyzed blood actively at room temperature (about 27 C.) or at 4 C. Hemolysis did not

TABLE 3.—*Comparison of Hemolytic Properties of Three Strains of Gram-Negative Bacilli*

		Origin of Bacillus								
		Patient's Blood			Transfused Blood			Transfused Blood		
Identification		Coliform Bacillus, Intermediate Type			Coliform Bacillus, Intermediate Type			Escherichia Freundii		
Hemolysis on blood agar at 37 C.		+			+			+		
Hemolysis in human whole blood at various temperatures		4 C.	27 C.	37 C.	4 C.	27 C.	37 C.	4 C.	27 C.	37 C.
Blood 1	24 hr.	—	—	—	±	±	+++	—	—	—
	48 hr.	—	—	±	+	+++	++++	—	—	—
	72 hr.	—	—	++	++	++++	++++	—	—	—
	96 hr.	—	+	++++	++	++++	++++	—	—	—
Blood 2	24 hr.	—	—	±	—	+++	++++	—	—	—
	48 hr.	—	±	++	++	++++	++++	—	—	—
	96 hr.	—	+	++++	++	++++	++++	±	±	+++
Blood 3	24 hr.	—	—	—	+	+++	++++	—	—	—
	48 hr.	—	±	++	++	++++	++++	—	—	—
	96 hr.	±	++	++++	++	++++	++++	±	—	—

TABLE 4.—*Minimal Inhibitory Concentrations of Antibiotics Required to Inhibit Growth of Each of Three Strains of Gram-Negative Bacilli Isolated During the Course of Transfusion Reaction*

		Antibiotics,* γ/Ml.				
Bacteria	Origin	A	C	T	S	P
Coliform of intermediate type	Patient's blood	0.1	0.4	0.4	25.6	0.4
Coliform of intermediate type	Bottle of contaminated blood	0.1	0.8	0.2	12.8	0.2
Escherichia freundii	Bottle of contaminated blood	0.4	3.2	0.8	25.8	0.4

* The antibiotics are abbreviated as follows: A, aureomycin; C, chloramphenicol; T, oxytetracycline (Terramycin); S, streptomycin; P, polymyxin B (Aerosporin).

appear in tubes of blood inoculated with E. freundii when they were incubated for four days at any of the three temperatures. The E. freundii, however, hemolyzed blood in agar at 37 C.

Sensitivity of the organisms to the bacteriostatic action of antibiotics was determined by a tube-dilution test used routinely in this laboratory.[3] In addition, the bactericidal action of the antibiotics was determined by subculturing into poured plates 0.1 ml. of antibiotic solution from tubes showing no visible growth after 24 hours. This was done to learn if the number of bacteria had been reduced from the original population of approximately 10^6 bacteria per 0.1 ml. The results for these tests are given in Tables 4 and 5.

3. Braude, A. I., and Dockrill, M.: Inaccuracies in the Disc Method for Determining Bacterial Sensitivity to Aureomycin Discovered by Comparison with the Tube-Dilution Method, J. Lab. & Clin. Med. **40**:149, 1952.

The sensitivities of the three strains of bacteria tested were essentially the same to all antibiotics when inhibition of growth was measured. Differences were observed, however, in their susceptibility to killing by these antibiotics. The three organisms were all resistant to streptomycin and inhibited by relatively small concentrations of polymyxin B, aureomycin, oxytetracyline (Terramycin), and chloramphenicol. Both aureomycin and oxytetracycline displayed a killing effect against each strain of coliform bacteria, although the coliform bacteria recovered from the blood in the bottle appeared to be killed by much lower concentrations of either antibiotic. Chloramphenicol was also found to kill the coliform bacillus isolated from the bottle of blood but not the coliform bacillus recovered from the patient. Polymyxin B did not kill the coliform bacillus from the bottle but was strongly bactericidal against the strain of coliform bacillus isolated from the patient and against the E. freundii. The strain of E. freundii, however, was killed by none of the other antibiotics.

TABLE 5.—*Bactericidal Effect of Antibiotics at 37 C. Against Three Gram-Negative Bacilli as Measured by Number of Surviving Bacteria per 0.1 Ml. of Antibiotic Solution* *

	Concentrations of Antibiotic, γ/Ml.									
	25.6	12.8	6.8	3.2	1.6	0.8	0.4	0.2	0.1	
Aureomycin	1	10	14	I	I	I	I	I	I	Coliform (P) †
	0	0	0	44	18	I	I	I	I	Coliform (B) †
	I	I	I	I	I	I	I	I	I	E. freundii
Chloramphenicol	I	I	I	I	I	I	I	I	I	Coliform (P)
	I	I	0	7	I	I	I	I	I	Coliform (B)
	I	I	I	I	I	I	I	I	I	E. freundii
Oxytetracycline (Terramycin)	81	I	I	I	I	I	I	I	I	Coliform (P)
	0	I	5	2	6	I	I	I	I	Coliform (B)
	I	I	I	I	I	I	I	I	I	E. freundii
Streptomycin	I	I	I	I	I	I	I	I	I	Coliform (P)
	I	I	I	I	I	I	I	I	I	Coliform (B)
	I	I	I	I	I	I	I	I	I	E. freundii
Polymyxin B (Aerosporin)	0	0	0	0	0	0	I	I	I	Coliform (P)
	I	I	I	I	I	I	I	I	I	Coliform (B)
	I	3	0	0	0	2	I	I	I	E. freundii

* Survival was determined in poured plates made 24 hours after inoculation of approximately 1,000,000 organisms into each 0.1 ml. of antibiotic solution.

† Abbreviations are as follows: I, innumerable; Coliform (P), bacillus isolated from patient; Coliform (B), bacillus isolated from bottle.

COMMENT

When certain Gram-negative bacilli invade the blood stream in overwhelming numbers, they bring about a syndrome typified by the present case. Transfusion of contaminated blood is a very rare cause of this syndrome. Bacteremic shock, induced by Gram-negative bacilli, usually occurs as a complication during the course of infections of the urinary tract, peritoneal cavity, female pelvic organs, lung, and subcutaneous tissues. Regardless of origin of the bacteremia, however, the outlook is always grave in spite of the best therapeutic efforts. Perhaps the crucial point in determining the outcome is prompt recognition of the syndrome. Unfortunately, the patient may not appear gravely ill during the first 12 hours after bacteremic shock begins and there are seldom outspoken signs to call attention to the serious state of hypotension.

There are three main manifestations. These are fever, hypotension, and pain, and they occur in that order. The outstanding symptoms at first are chills, fever,

and sweats. Two or more febrile paroxysms may occur daily. When bacilli are injected, as in transfusion of contaminated blood, there is a latent period followed by chills and then fever. In this case the latent period was about 30 minutes. The fever is accompanied by polymorphonuclear leucocytosis.[4]

The first circulatory effect observable is a slight elevation of blood pressure at the time of the chill.[4] This is followed by a fast drop in blood pressure. This patient's blood pressure fell to 86/70 within two hours after the chills began and in six hours had reached 70/40. The hypotension is accompanied by restlessness, hyperventilation, slight cyanosis, and apprehension. During the first 12 hours these signs are only slight but later become severe. Anuria is also present.

Pain is in both abdomen and extremities. It is chiefly due to great muscular overactivity. Severe vomiting and diarrhea reflect intense activity of intestinal musculature; the rigors, of the peripheral musculature. The pain is accompanied by excruciating tenderness to touch and makes nursing difficult because the patient can not be handled easily.

The anuria, vomiting, and diarrhea are important factors in the rapid development of acidosis and uremia. In this case the nonprotein nitrogen had risen to 64 mg. per 100 cc. and the CO_2 dropped to 22 vol. % in 24 hours. The nonprotein nitrogen continued to rise, even after the urinary output returned to normal, and reached 118 mg. per 100 cc. by the fifth day.

Treatment must be directed at the cause as well as the manifestations of the bacteremia. In bacterial transfusion reactions the cause may be determined quickly by examining a direct smear of the blood from the transfusion bottle. Gram-negative bacilli will be found in each microscopic field. There is no time to wait for identification of these gram-negative bacilli, or for sensitivity tests. Treatment must be established that will prevent new bacilli from growing and producing endotoxin, while the effects of those originally introduced can be counteracted. It is desirable not only to inhibit growth but also to eradicate all living bacilli as quickly as possible. There should be no hesitation, therefore, in using all antibiotics which may exert antibacterial effects against Gram-negative bacilli.

This patient was promptly treated with polymyxin B, aureomycin, chloramphenicol, and penicillin. Subsequent studies bore out the logic of using several antibiotics. Polymyxin B proved to be highly bactericidal against the E. freundii and the coliform bacillus isolated from the patient but not against the coliform bacillus in the bottle. Aureomycin, on the other hand, proved bactericidal for both coliform bacilli, but not for the E. freundii. Within 16 hours after treatment with antibiotics was started, the patient's blood had been sterilized. At the start of therapy bacteremia was so great that it was impossible to count the total number of colonies in a millimeter of blood. Fortunately, the antibiotics were active against these bacteria. In general, polymyxin B has probably the widest range of activity against Gram-negative bacilli. It is remarkably effective in combating Ps. aeruginosa, but it is ineffective against strains of Proteus. Proteus constitutes a major problem in bacterial chemotherapy. At present, no antibiotics or chemotherapeutic agents are outstanding in their action against that organism. In our laboratory, chloramphenicol has shown the most consistent ability to inhibit Proteus, although the effective

4. Bennett, I. L., Jr., and Beeson, P. B.: The Properties and Biologic Effects of Bacterial Pyrogens, Medicine **29**:365, 1950.

concentrations have tended to be higher than those usually attainable in the blood. Waisbren [5] has observed an additive, and, sometimes, synergistic action against Proteus when chloramphenicol is combined with penicillin. Both agents were used here to cover the possibility of a proteus bacteremia. Sulfisoxazole (Gantrisin) and neomycin have also shown action against Proteus.

The hypotension was treated by arterenol. The amount required was far greater than that ordinarily recommended for treating shock. Our patient received 80 mg. on the second day and 96 mg. on the third day. Kurland and Malach,[6] who treated 30 patients with intravenous injection of arterenol for shock due to a variety of causes, gave a maximum total dose of 62 mg. during a period of five days, or about 12 mg. per day. Wise, Shaffer, and Spink,[7] on the other hand, have administered 136 mg. in a single daily dose to a patient in shock resulting from bacteremia due to Gram-negative bacilli. The doses required for our patient testify to the profound and persistent nature of the hypotension. When enough arterenol was being injected, the blood pressure was promptly restored and the restlessness, apprehension, confusion, and hyperventilation of the hypotensive state disappeared. Furthermore, urinary output was restored. Gradual reduction in concentration of arterenol permitted eventual weaning of the patient from arterenol. The cause of the shock had undoubtedly been eliminated by then. The only apparent ill effect from the arterenol was phlebitis at the site of injection.

The value of the cortisone was not clear. Kurland and Freedberg [8] have found that cortisone and corticotropin potentiate the pressor response to arterenol under experimental conditions. Bacterial pyrogens have an adrenocortex-stimulating effect which may be adequate in itself.

Close attention during treatment must be paid to the changes in electrolyte concentrations. Inorganic acids appear to accumulate rapidly following the excessive destruction of body proteins during the complete anuria. The CO_2 falls sharply in 24 hours. Because of vomiting and diarrhea, chlorides and sodium are also depleted. One-sixth molar lactate, sodium bicarbonate solution and isotonic sodium chloride solution were all used in appropriate quantities to restore electrolyte equilibrium.

The source of the contamination was investigated and found to be related to the accidental use of contaminated syringes for withdrawing blood from the bottles to obtain specimens for the Kahn test. Many of these syringes had been used to enter bottles of blood without reactions having occurred. Undoubtedly many bloods were

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contaminated in this way, but the bactericidal or bacterial-suppressive action of many bloods, as well as the slow rate of bacterial growth in blood in the refrigerator, protected most recipients.[9]

In this case, a large inoculum of the contaminating bacteria was unable to multiply during storage at 4 C. for one week in a second sample of citrated blood, obtained after the reaction, from the original donor. Even at room temperature, the donor's blood entirely suppressed small inoculums for one week, and for six hours appeared to possess bactericidal properties. By 24 hours, however, heavy growth at room temperature did occur in the donor's blood. The number of contaminating bacteria introduced originally was probably great enough, therefore, to produce the observed clinical effects without growth. It is also possible that the blood remained for 24 hours at room temperature sometime after it became contaminated and that a large inoculum was thus permitted to grow.

One of the bacilli, the coliform, was hemolytic in blood at 4 C. Although no signs of a hemolytic reaction were observed, refrigeration of the contaminated blood for several days after the reaction led to hemolysis.

Undoubtedly, the coliform bacillus isolated from the patient was the same as, or a closely derived variant of, the coliform bacillus present in the contaminated bottle. The differences between the two strains suggest that variation had been brought about by passage through a host.

Slight hope was held that the induced bacteremia might be beneficial to the patient. This hope was based on the known necrotizing effect of Serratia marcescens on tumors, and a similar effect on this patient's neoplastic disease was considered possible.[10] No beneficial effect materialized.

SUMMARY

A patient suffered a bacterial transfusion reaction due to Gram-negative bacilli. He was treated with antibiotics, arterenol, and cortisone and recovered from the acute episode. The patient later died of Hodgkin's disease.

The three chief clinical characteristics of the transfusion reaction were fever, hypotension, and pain. Uremia, secondary to anuria, was the most prominent complication.

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PULMONARY MANIFESTATIONS OF SCLERODERMA

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SCLERODERMA was once thought to be a disease limited to the skin, but recent reports have emphasized involvement of the gastrointestinal tract,[1] heart,[2] lungs,[3] kidneys,[4] endocrine glands, bones, and skeletal muscle.[1] It is now thought that scleroderma is a systemic disease, and Goetz [5] has suggested that a more appropriate name would be progressive systemic sclerosis, of which skin involvement is only one manifestation.

In the early descriptions of generalized scleroderma, dyspnea and a tendency to pulmonary infections were attributed to restrictions of respiratory movements produced by sclerotic changes in the skin and muscles of the chest wall. Now it seems more likely that the pulmonary symptoms are due to fibrotic changes in the lungs. In 1891 Finlay [6] recognized the association between scleroderma and pulmonary fibrosis, while Lewin and Heller,[7] in 1895, and later Matsui [8] demonstrated pulmonary fibrosis at autopsy in cases of scleroderma. The roentgenological features

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of pulmonary fibrosis due to generalized scleroderma were first correlated by Murphy, Krainin, and Gerson,[3d] in 1941. Since that time there have been several other reports, the most recent being that of Hayman and Hunt,[3c] who reported 1 case and reviewed 27 cases from the literature of pulmonary scleroderma roentgenographically visualized.

This report is based on a study of 37 patients for whom a clinical diagnosis of scleroderma was established. Five patients had abnormal chest roentgenograms. In four of these the diagnosis was supported by histological evidence. The roentgen findings in this group were strikingly similar and consisted of a diffuse, linear, interstitial infiltration, more marked in the lower half of both lung fields. Because of the uniformity of the roentgenological pattern it was felt that these cases were worthy of reporting. Knowledge of the pulmonary changes occurring in scleroderma is of particular importance, since they may precede the onset of the characteristic skin lesions. The roentgenographic findings are similar to those described in the literature and constitute a fairly typical appearance, with which the roentgenologist and clinician should be familiar. A sixth case, in which initial chest roentgenograms showed no abnormalities, is included because of the development of terminal pulmonary edema.

REPORT OF CASES

CASE 1.—R. H., a 46-year-old white coal miner, entered Barnes Hospital in April 1950, because of joint pains for three years. Five years earlier he began to lose weight and experience malaise without cough or fever developed. A chest roentgenogram was interpreted as abnormal, and the patient was admitted to a sanatorium, where he was treated with bed rest for 10 months, with complete relief of symptoms. No diagnosis was established. Two years later he noted that his fingers and toes turned blue in cold weather. During the next two years progressive stiffness and disability of the fingers associated with weight loss resulted in a diagnosis of rheumatoid arthritis. One year before entry the patient was forced to stop work because of marked weakness. The skin over the joints of the extremities and face became tight, shiny, and hard, and areas of ulceration appeared on the legs. Roentgen examination of the chest revealed coarse and fine linear streaks of infiltration throughout both lung fields. The heart was not enlarged (Fig. 1). Six months prior to entry the patient experienced dyspnea, orthopnea, ankle edema, and dysphagia. There was no significant cough or chest pain.

Physical examination on hospital admission revealed an afebrile emaciated man with indurated shiny skin over the face, hands, feet, and knees. The positive findings included marked limitation of motion of all joints, considerable muscular atrophy, and fine rales over both lung bases. Heart sounds were of poor quality, and a moderate precordial systolic murmur was heard. The blood pressure was 105/70.

A complete blood examination gave normal results. Urinalysis revealed a faint trace of albumin, with occasional red and white blood cells in the sediment. The blood Kahn reaction was positive. Venous pressure in the antecubital vein was 170 mm. of saline, and the circulation time from arm to tongue was 26 seconds. Culture of the sputum was consistently negative for tubercle bacilli. An electrocardiogram was interpreted as showing an abnormal form of ventricular complex, incomplete right bundle branch block, and left axis deviation. Roentgen examination of the chest at this time showed no change in the appearance of the diffuse interstitial fibrosis. The heart was somewhat larger than before, with a small amount of fluid in both costophrenic angles. Examination of the esophagus showed absence of peristaltic activity in the distal half.

A diagnosis of scleroderma heart disease and mild congestive failure was made, and the patient was given digitalis without significant improvement. Fever did not occur at any time. On the 12th hospital day the patient suddenly stopped breathing and died.

Fig. 1 (Case 1, R. H.).—Roentgenogram of the chest taken in 1949, showing coarse and fine linear streaks of parenchymal infiltration dispersed throughout both lung fields.

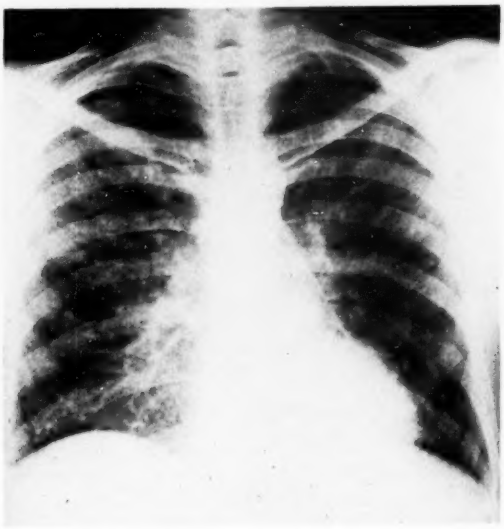

Fig. 2 (Case 2, E. F.).—Chest roentgenogram taken in April 1952, revealing a diffuse linear interstitial infiltration, somewhat more marked in the lower two-thirds of both lungs, compatible with the appearance of interstitial fibrosis.

Autopsy Findings.—At autopsy thickened skin with absence of the normal cutaneous furrows was found on the face, thorax, hands, and fingers. Four hundred fifty cubic centimeters of turbid yellow fluid was found in the right pleural cavity, and 150 cc. in the left. The lungs weighed 1750 gm. and from cut sections exuded dark frothy fluid. The interlobular septa were thickened and prominent, and microscopic examination revealed a diffuse fibrosis of the alveolar walls.

The heart was enlarged, weighing 470 gm. The right ventricular wall measured 4 mm., and the left ventricular wall measured 10 mm. The coronary arteries were widely patent, without sclerotic plaques. There was microscopic evidence of diffuse myocardial fibrosis.

Case 2.—E. F., a 31-year-old white man, was admitted to Barnes Hospital in April 1952. In 1942 he had been rejected by the Army because of an abnormal chest x-ray, although he was asymptomatic at the time. In 1947 there was an insidious onset of asthenia, fatigue, malaise, productive cough, and loss of 30 lb. (13.5 kg.). In October 1950 the patient entered a sanatorium. He was placed on a regimen of bed rest, and cough disappeared and he gained 40 lb. (18 kg.). Chest roentgenograms revealed a diffuse linear interstitial infiltration, somewhat more marked in the lower two-thirds of both lungs. No evidence of tuberculosis was found. Skin tests for histoplasmosis, blastomycosis, and coccidioidomycosis were allegedly negative. Several months before entry to Barnes Hospital the patient noted return of weakness, fatigability, and cough productive of white sputum without fever or hemoptysis. For the first time he noted dyspnea on exertion. On direct questioning a history of mild dysphagia of six months' duration was obtained.

Physical examination revealed a chronically ill man with slight cyanosis of the face and neck. The skin over the face and hands was tight, shiny, and parched. There were dilated superficial veins over the anterior chest and medium rales at both lung bases. The blood pressure was 115/60. The remainder of the physical examination showed no abnormalities.

The red and white blood cell counts were normal. Sputum cultures were negative for tubercle bacilli. An electrocardiogram was interpreted as showing an abnormal form of ventricular complex with a question of left ventricular enlargement. Roentgen examination of the chest revealed coarse and fine linear streaks throughout both lung fields (Fig. 2), which in comparison with previous films showed no change. The heart was not enlarged. Bronchograms showed slight but definite cylindrical dilatation of the terminal bronchioles. A gastrointestinal study showed absence of peristaltic activity in the distal esophagus. X-ray examination of the joints and the teeth showed no abnormalities. Skin biopsy showed hyperkeratosis without atrophy. The collagen bundles of the dermis were swollen and homogeneous. Blood vessel walls were thickened with a moderate perivascular infiltration. The biopsy specimen was interpreted as showing changes compatible with scleroderma.

Throughout the entire hospital stay the temperature was within normal limits. It seemed likely that the clinical and roentgenographic findings could be due to visceral scleroderma.

Case 3.—H. M., a 56-year-old white man, was admitted to Barnes Hospital for the second time in May 1952. His illness began in 1941, when painful cyanosis of the extremities on exposure to cold, aching pains in both calves, arthralgia, and occasional intermittent chest pains developed. These symptoms continued, and over the next two years progressive stiffness of the fingers developed and the patient lost 40 lb. (18 kg.). In 1943 the patient entered Barnes Hospital with characteristic findings of scleroderma of the face and hands. A skin biopsy, which showed edematous swollen collagen, hyperkeratosis, and thickening of the blood vessel walls, confirmed this clinical impression. Roentgenographic examination of the chest showed a diffuse linear arborizing infiltration throughout both lung fields, with prominent hilar shadows. The heart size was within the upper limits of normal (Fig. 3*A*).

The patient was discharged and followed in the outpatient department, where he was treated with thyroid medication without noticeable improvement. He was relatively asymptomatic until 1949, when progressive dyspnea developed. A second chest roentgenogram demonstrated no change in the interstitial pulmonary infiltration.

In May 1952 he was admitted to the surgical ward because of sudden pain and discoloration in the tip of the index finger. There were no other symptoms except slight dyspnea and dysphagia.

At this time he exhibited obvious advanced changes of scleroderma of the hands, forearms, and face, with increased pigmentation and vitiligo. Examination of the chest revealed an increased anteroposterior diameter and fine dry rales at both lung bases. The heart was not enlarged. The heart rhythm was regular, and the sounds were of good quality, without murmurs. The blood pressure was 120/80.

Routine laboratory data showed no abnormalities. Tuberculin tests with first and second strength purified protein derivative were negative. Venous pressure, circulation time, and electrocardiogram were within normal limits. A chest roentgenogram showed no change in the appearance of the lungs since the previous examination, in 1943 (Fig. 3*B*). Examination of the esophagus revealed absence of peristaltic activity in the distal half.

CASE 4.—C. S., a 68-year-old white laborer, entered Barnes Hospital for the second time in September 1952. He was in good health until 1946, when he noted exertional dyspnea and a slightly productive cough. The dyspnea remained unchanged until 1950, when it became more severe and was associated with ankle edema. In 1951 subcutaneous swelling, dermal thickening, and tightness appeared in the fingers, face, and hands. Flexion deformities of the

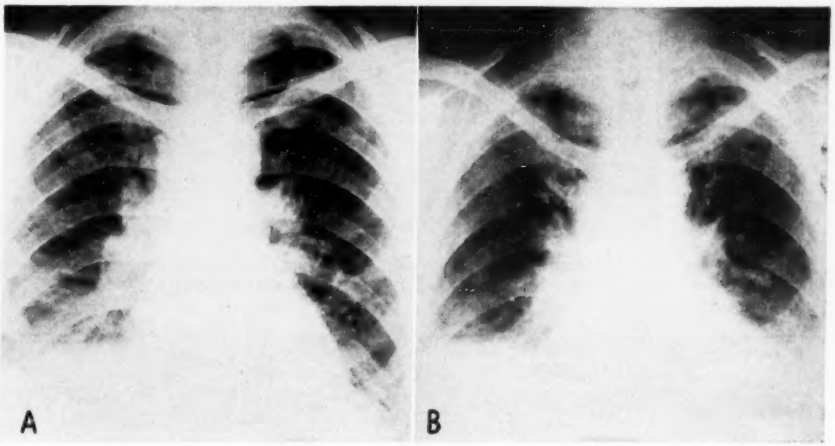

Fig. 3 (Case 3, H. M.).—*A*, chest roentgenogram taken in 1943, revealing a diffuse reticulated infiltration involving the lower two-thirds of both lung fields, with prominent hilar shadows suggesting lymph node enlargement. *B*, roentgenogram taken nine years later, revealing no change in the interstital fibrosis.

fingers followed, and the patient noted that his fingers and toes became blue and painful on exposure to cold. Minimal dysphagia was admitted on direct questioning.

At the time of the patient's first hospitalization, in May 1952, physical examination revealed a man who appeared chronically ill. The skin over the fingers and face was indurated and hyperpigmented. Expiratory wheezes were present over the anterior chest. The heart was enlarged, with a Grade 2 apical systolic murmur. The blood pressure was 130/60. Moderate pretibial edema was present.

Admission laboratory tests revealed a moderate anemia. The electrocardiogram showed only borderline low voltage. A skin biopsy was interpreted as showing scleroderma. Roentgen examination of the chest revealed a diffuse interstitial pulmonary fibrosis, with moderate left ventricular cardiac enlargement. Periarticular calcifications were noted in the hands. Roentgen examination of the esophagus revealed absence of peristalsis in the distal half.

On the patient's second hospital entry he was thought to be in mild congestive failure and was treated with diuretics and digitalis with some response. A second chest roentgenogram, in February 1953, demonstrated no change in the pulmonary fibrosis or in heart size (Fig. 4).

CASE 5 (Courtesy of Dr. S. E. Shechter).—I. G., a 43-year-old man, was first seen in November 1950, complaining of mild dysphagia of one month's duration. Physical examination was negative. Laboratory studies, including blood counts, urinalysis, and Kahn test showed no abnormalities, except for a slight eosinophilia. A gastrointestinal examination performed elsewhere was interpreted as showing questionable cardiospasm. Roentgen examination of

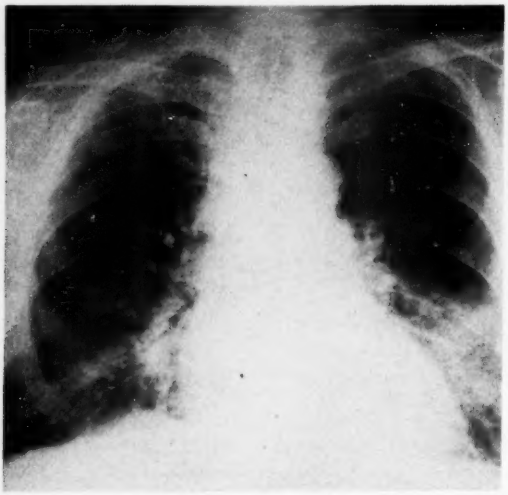

Fig. 4 (Case 4).—The roentgenogram shows diffuse linear interstitial infiltration in both lower lung fields, with evidence of moderate left ventricular cardiac enlargement.

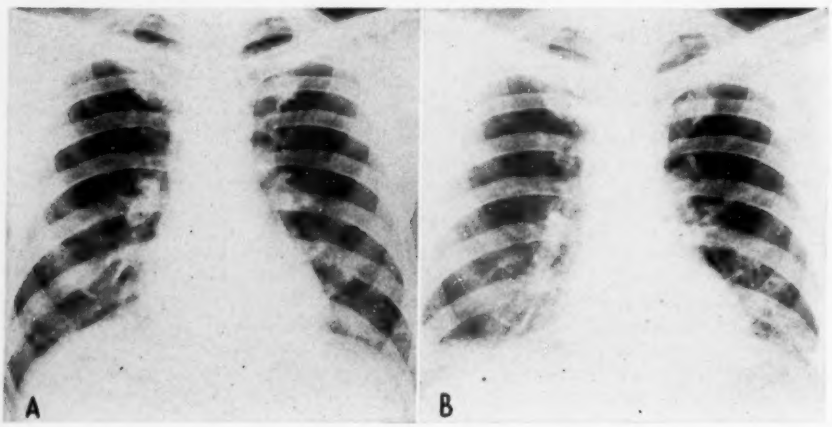

Fig. 5 (Case 5).—*A*, roentgenogram taken November 1950, showing a diffuse fibrous network throughout both lung fields, more marked in the lower half. *B*, roentgenogram taken nine months later, showing an increase in the linear basilar infiltration. The patient denied any respiratory complaints.

the chest revealed a diffuse fibrous network throughout both lungs, more marked at the bases (Fig. 5*A*).

Nine months later, in July 1951, a second roentgenogram of the chest (Fig. 5*B*) showed an increase in the basilar infiltration, although the patient denied any respiratory symp-

toms. Ten months after the first examination, an area of thickened, shiny, slightly pigmented skin appeared over the upper anterior chest, and the patient mentioned a few episodes of numbness in his fingers. There were no symptoms referable to the respiratory system. A chest roentgenogram showed no change in the character of the pulmonary infiltration.

The patient was started on cortisone therapy that resulted in some transient improvement in the skin, but during the next six months the area of thickened skin extended onto the lower neck and the upper back.

Reexamination of the chest, in April 1952, revealed no change in the chest roentgenogram. In May 1952 the skin changes had almost completely disappeared, although the mild dysphagia persisted.

CLINICAL CONSIDERATIONS

The clinical findings in these five cases of scleroderma are summarized in the Table. One of the most significant aspects of the clinical picture is that the pulmonary involvement may precede the cutaneous manifestations and thus obscure the correct diagnosis. In 7 of 27 cases in the literature reviewed by Hayman and Hunt,[3c] symptoms of pulmonary scleroderma were present before the development of definite cutaneous manifestations. This was also true for four of the five patients

Summary of Clinical Findings in Five Cases of Scleroderma with Pulmonary Involvement

Patient	Sex	Age, Yr.	Duration of Disease Yr.	Duration of Pulmonary Symptoms, Yr.	Initial Symptoms	Cough	Dyspnea	Cardiac Enlargement	Dysphagia	Esophagus Involvement
R. H.	M	41	5	½	Constitutional	−	+	+	+	+
E. F.	M	26	5	5	Constitutional	+	+	−	+	+
H. M.	M	45	11	3	Raynaud's phenomenon	−	+	−	+	+
C. S.	M	61	7	7	Cough and dyspnea	+	+	+	+	+
I. G.	M	41	3	0	Dysphagia	−	−	−	+	+

described above. Two patients (Cases 1 and 2) were thought to have pulmonary tuberculosis and were admitted to a sanatorium for treatment. The chief pulmonary symptoms were dyspnea and cough, but they usually did not occur until the pulmonary changes were advanced. One patient (Case 5) has been followed for two years without any pulmonary complaints despite roentgenographic evidence of progression of the pulmonary fibrosis. There apparently is no correlation between the severity of the skin changes and the degree of pulmonary involvement. This lack of correlation is also true for cardiac involvement, according to Weiss and his associates.[2]

Raynaud's phenomenon or acrosclerosis was present in four of the five cases but preceded the pulmonary involvement in only one instance (Case 3). Mild dysphagia was present in all cases and was the chief complaint in one (Case 5). All five cases showed absence or impairment of peristaltic activity in the distal half of the esophagus, without evidence of stricture.

In none of the cases could a diagnosis of cor pulmonale be established. Two cases showed moderate left ventricular cardiac enlargement. Because of the absence of hypertension and other etiological factors, the presence of scleroderma heart disease was suspected in two cases and confirmed in one case at autopsy (Case 1). Review of the other 32 cases of scleroderma studied at Barnes Hospital revealed

pulmonary symptoms (cough, sputum production, and dyspnea) to be present in 14. The roentgen examination of the chest in this group showed no abnormalities, except for bizarre thinning of several of the posterior ribs in one patient.

PATHOLOGY

The fundamental disturbance in scleroderma seems to be an abnormal change in the collagen, and consequently it has been included in the group of "diffuse collagen diseases" that also includes lupus erythematosis, dermatomyositis, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, thromboangiitis obliterans, and arteriolosclerosis.[9] This grouping is based on the demonstration that the characteristic pathological changes occur in fibrous connective tissue. These consist of a cellular perivascular infiltration, fibrous proliferation, and the occurrence of a myxomatous swelling of the collagenous ground substance of the connective tissue, which assumes an appearance like fibrin, hence the term fibrinoid degeneration. The myxomatous swelling of the collagen is followed by transient lymphocytic and mononuclear infiltration. The collagen fibers become thickened, and new ones are formed, which partly accounts for the tissue induration. Degeneration and fragmentation of elastic tissue and muscle occur. Great proliferative activity may occur in the absence of fibrinoid necrosis in the immediate vicinity.

Thus the pathological process exhibits three principal aspects,[10] the degenerative or destructive alterations, as represented by the fibrinoid necrosis; the proliferative changes, which result in masses of dense connective tissue, and the inflammatory reaction to the primary connective tissue injury. In the different diseases usually included in the collagen group, according to Duff,[10] there are considerable differences in the degree to which each of these pathological processes manifests itself. These differences, together with differences in the anatomical distribution of the lesions, permit recognition of distinct disease entities on pathological as well as clinical grounds.

The occurrence of similar changes in anaphylactic lesions of the lungs and other organs, both experimentally produced in animals and as found at autopsy in patients with serum sickness, has been held to support the allergic theory of the etiology of these diseases. Klemperer[9] and others have pointed out that this anatomical feature does not imply a pathogenetic relationship among these various diseases. Fibrinoid changes in collagen also occur in chronic inflammations, sarcoidosis, tuberculosis, malignant and experimentally produced hypertension, in the base of peptic ulcers, in the vicinity of foreign bodies and abscesses, in regional enteritis, in myxedema, and in malignant lymphoma. According to Klemperer it is merely a form of degeneration that occurs in a wide variety of dissimilar diseases.

In scleroderma the most constant lesions are proliferative, with the production of dense collagenous tissue with little or no inflammatory reaction, and fibrinoid necrosis may or may not be present. In the lungs of one patient (Case 1), there was extensive fibrous thickening of the alveolar walls, with an increase in bulk and density of the connective tissue. According to Hayman and Hunt[3c] the principal pathological change found in the lungs in the seven autopsied patients

9. Klemperer, P.: Concept of Collagen Disease, Am. J. Path. **26**:505, 1950.

10. Duff, G. L.: The Diffuse Collagen Diseases: Morphological Correlation, Canad. M. A. J. **58**:317, 1948.

reported in the literature in whom pulmonary involvement was demonstrated roentgenographically was a sclerosing alteration of the collagen framework corresponding to that which we have described. These changes interfere with oxygen diffusion across the alveolocapillary membrane and fall into the physiopathologic pattern which has been termed diffusion fibrosis.[11] Physiologic studies reveal a normal or slightly reduced arterial oxygen saturation at rest but a marked drop after exercise.[12] Pulmonary hypertension may result from an anatomic reduction in the capacity of the pulmonary vascular bed. These patients frequently die of pulmonary insufficiency before chronic cor pulmonale has developed. Cor pulmonale did not occur in any of our patients nor in the cases of pulmonary scleroderma described in the literature.

A second type of lung change consists of subpleural cyst formation, probably due either to the dissolution of alveolar walls, or to obstructive emphysema, or to a combination of both. Widespread bronchiolectasis, which may be the result of the diffuse peribronchial fibrosis and atrophy of the bronchial musculature, has been described.

ROENTGENOGRAPHIC CONSIDERATIONS

Pugh, Kvale, and Margulies[13] stated that "the pulmonary lesions of scleroderma seem to have a rather distinctive roentgenographic appearance but this defies adequate description." They felt that in many cases the roentgenologic diagnosis of pulmonary scleroderma could be made without knowledge of the clinical picture. In the five cases reported above a rather striking similarity in the roentgenographic appearance was present, consisting of a widespread linear reticulated infiltration which was more marked in the lower half of the lung fields.

The differential diagnosis of diffuse pulmonary lesions is extremely difficult. Felson and Heublein[14] listed 79 conditions that can be responsible for diffuse pulmonary lesions. The conditions that may cause the greatest difficulties in differential diagnosis, from the roentgenographic aspect, are sarcoid, lymphangitic carcinomatosis of the lung, pulmonary congestion, and pulmonary fibrosis due to other causes. Pulmonary sarcoidosis is usually associated with bilateral hilar adenopathy, which is rare in scleroderma, although one of our patients (Case 3) did have prominent hilar shadows suggesting lymph node enlargement. When scleroderma heart disease is present, the differentiation between pulmonary congestion and fibrosis may be extremely difficult, if not impossible. In general, fibrosis tends to be more linear and discrete than the fuzzy vascular markings seen in congestive failure.

We have been particularly interested in determining whether the disease entities included in the collagen group could be distinguished from each other on

11. Baldwin, E. deF.; Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: A Study of 39 Cases of Pulmonary Fibrosis, Medicine **28**:1, 1949.

12. Harvey, R. M.; Ferrer, M. I.; Richards, D. W., Jr., and Cournand, A.: Influence of Chronic Pulmonary Disease on the Heart and Circulation, Am. J. Med. **10**:719, 1951.

13. Pugh, D. G.; Kvale, W. F .,and Margulies, H.: Scleroderma with Involvement of the Viscera: Report of Case, Proc. Staff Meet., Mayo Clin. **20**:410, 1945.

14. Felson, H., and Heublein, G. W.: Some Observations on Diffuse Pulmonary Lesions, Am. J. Roentgenol. **59**:59, 1948.

the basis of the roentgenographic changes in the lungs. Sante and Wyatt [15] divided the collagen diseases into two major roentgenological groups on the basis of whether or not antigenic (azotemic) pulmonary edema was present. The conditions in which antigenic pulmonary edema was found included anaphylaxis, acute glomerulonephritis, and polyarteritis nodosa. In the second group, which included acute disseminated lupus, scleroderma, rheumatic pneumonia, and dermatomyositis, antigenic pulmonary edema did not occur and the roentgen manifestations consisted only of irregular collagenous deposits throughout the lung fields.

We feel that when the pathological and clinical findings are correlated with the roentgenographic appearance, a more precise differential diagnosis may be possible. Acute pulmonary edema (antigenic pulmonary edema, azotemic edema) consisting of bilateral, homogeneous, central areas of increased density, with sparing of the apices, bases, and periphery, does occur with varying frequency in the collagen group of diseases. However, we feel that this type of pulmonary reaction may represent a complication of the disease and does not reflect the primary pathological process. The following case of scleroderma, in which pulmonary edema developed during a terminal episode of renal failure, illustrates this point.

Case 6 (This case was previously the subject of a clinicopathologic conference published in *The American Journal of Medicine* [16]).—E. L., a 49-year-old white laborer, was first admitted to Barnes Hospital in December 1951, because of stiffness of the skin and weakness. One year before, he had noted the insidious onset of anorexia. Four months later painful swellings and tightness of the skin appeared on the chest and face and over the joints of the upper and lower extremities. Two months before the patient's hospitalization his hands became blue and painful on exposure to cold and small ulcers developed on the finger tips. There was no dysphagia or cardiac symptoms. The patient had lost 25 lb. (11.25 kg.) since the onset of his illness.

On physical examination the skin over the face, neck, chest, and extremities was found to be indurated, with limitation of movement of the joints. Routine laboratory studies showed no abnormalities. A skin biopsy revealed changes compatible with scleroderma. Roentgenographic examination of the chest (Fig. 6*A*) and esophagus showed no abnormalities.

The second hospital entry, in May 1952, followed a three-day episode of dyspnea, orthopnea, cough, and hemoptysis. Physical examination at this time revealed a blood pressure of 190/100 mm., a respiratory rate of 40, and a pulse rate of 140. There was no fever at this time. The patient was orthopneic, and mildly cyanotic and appeared critically ill. The skin on the face, hands, and feet now showed areas of brown pigmentation, with 2+ pedal edema. The retinal arteries were markedly narrowed, with scattered hemorrhages and exudates. Rales were heard over the lower portions of both lung fields. The heart was not enlarged, and no murmurs were heard. A diastolic gallop was present. Blood examination revealed a moderate anemia. Urinalysis showed a specific gravity of 1.008, albuminuria 2+, and an occasional granular cast, with white and red cells in the sediment. The nonprotein nitrogen was 52 mg. per 100 cc. Roentgenograms of the chest revealed bilateral areas of homogeneous density, with a relatively clear periphery that was interpreted as pulmonary edema (Fig. 6*B*). The electrocardiogram was interpreted as showing a left ventricular strain pattern and sinus tachycardia. The patient was treated with digitalis, aminophyllin, and oxygen, which resulted in less orthopnea but in no change in the tachycardia. During the first two hospital days the temperature rose to 38.8 C. but promptly subsided with antibiotic therapy. The urinary output diminished markedly. On the third hospital day the blood nonprotein nitro-

15. Sante, L. R., and Wyatt, J. P.: Roentgenological and Pathological Observations in Antigenic Pneumonitis: Its Relationship to Collagen Diseases, Am. J. Roentgenol. **66**:527, 1951.

16. Clinico-Pathologic Conference: Scleroderma with Congestive Heart Failure, edited by R. J. Glaser, and D. E. Smith, Am. J. Med. **14**:231, 1953.

gen was 110 mg. per 100 cc. An electrocardiogram showed only digitalis effect. Cortisone and 5 units of packed red blood cells were given. On the sixth hospital day the urinary output fell to 100 cc., while the nonprotein nitrogen rose to 164 mg. per 100 cc. The patient gradually became obtunded and died suddenly.

At autopsy the histologic examination of the lungs revealed two interesting features. In the alveolar walls a marked connective tissue proliferation with a few scattered mononuclear cells was found. In addition, accumulations of fibrin clumps and red blood cells were present in the alveolar spaces. The connective tissue proliferation was interpreted by the pathologist as representing scleroderma involvement of the lung in the absence of chronic heart disease and passive congestion. The presence of the fresh fibrin and red cells in the alveolar spaces was believed to be more likely related to the terminal episode of acute pulmonary edema.

The kidney weighed 150 gm. and presented a pale yellow surface mottled with red foci confined to the cortex. Micrscopically there was intimal fibrosis and fibrinoid alteration of the intralobular arteries. The afferent arterioles and an occasional glomerular tuft exhibited fibrinoid necrosis. There were numerous small recent infarcts of the cortex.

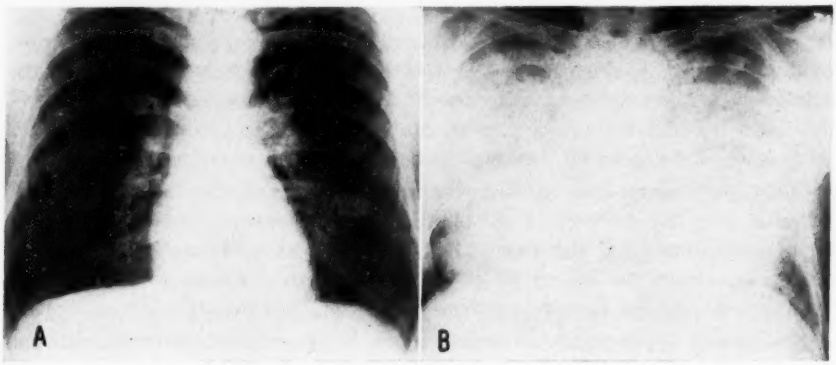

Fig. 6 (Case 6, E. L.).—*A*, initial chest roentgenogram taken before onset of terminal renal failure, revealing clear lung fields. *B*, roentgenogram after development of respiratory distress, showing large zones of increased density with irregular outlines and a "butterfly" distribution located in the perihilar regions of both lung fields. This appearance is characteristic of pulmonary edema.

COMMENT

It is interesting that the lung showed no roentgenographic abnormalities prior to the onset of pulmonary edema although there was microscopic evidence of interstitial fibrosis. Moore and Sheehan [4] have recently pointed out that it is not generally recognized that renal failure may be the cause of death in scleroderma. They described a specific histologic type of renal lesion, which occurred in three patients, consisting of dilatation of the intralobular arteries with fibrinoid necrosis of the smaller arterioles resulting in ischemia of the renal cortex and oliguric uremia. A review of the other 32 cases from this institution showed renal insufficiency to be the cause of death in five patients.

The pulmonary manifestations of disseminated lupus erythematosus usually consist only of a pleural effusion. Rakov and Taylor [17] and Foldes [18] have described

17. Rakov, H. L., and Taylor, J. S.: Acute Disseminated Lupus Erythematosus Without Cutaneous Manifestations and with Heretofore Undescribed Pulmonary Lesions, Arch. Int. Med. **70**:88, 1942.

18. Foldes, J.: Acute Systemic Lupus Erythematosus, Am. J. Clin. Path. **16**:160, 1946.

a chronic interstitial pneumonitis which leads to atelectasis and may cause respiratory failure. Baggenstoss [19] confirmed this observation and also noted a mucinous interstitial edema, which may be the precursor of the interstitial pneumonitis. Thorell [20] claimed that a subpleural finely mottled and streaked parenchymal infiltration associated with a small pleural effusion was characteristic and should suggest the diagnosis of disseminated lupus. Our experience with this condition suggests that parenchymal involvement is rare, and when it does occur tends to resemble an atypical pulmonary edema.

According to reports in the literature the incidence of pulmonary involvement in polyarteritis nodosa is 25%.[21] The pulmonary manifestations vary, depending upon whether the lesions are acute or chronic, gross or microscopic, isolated or confluent. Consequently the roentgen appearance may range from showing no abnormality to showing evidence of a diffuse miliary and nodular infiltration. If the lesions coalesce a pneumonic type of consolidation results, whereas involvement of a large artery may produce extensive infarction with necrosis and cavitation. The only characteristic feature of the roentgenogram is that it is constantly changing.[22] Although at some phase of the disease it may simulate the pulmonary manifestations of scleroderma, the latter differs by the constancy of the lesions. Serial roentgenograms in cases of polyarteritis will disclose lesions progressing and regressing, new lesions appearing, and others healing.

Pulmonary edema may occur during the course of polyarteritis. Here too we feel that this may represent a complication that is superimposed on the underlying basic pathological alterations. In a recent report by Doub,[23] hilar enlargement was a common finding in cases of polyarteritis nodosa with pulmonary involvement, whereas in our experience this is unusual in scleroderma.

Pulmonary involvement is quite unusual in rheumatoid arthritis, although several instances have been described in the literature.[24] The roentgen appearance has been described as a diffuse mottling resembling miliary tuberculosis but tending to completely resolve. In two cases in which autopsy was done, reported by Ellman and Ball,[24b] interstitial pneumonitis with well-marked fibrinoid necrosis in the alveolar walls was observed. Because of the occasional occurrence of red swollen joints early in the course of scleroderma, it is conceivable that scleroderma could be confused with rheumatoid arthritis.

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19. Baggenstoss, A. H.: Visceral Lesions in Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **27**:412, 1952.

20. Thorell, I.: Pulmonary Changes in Cases of Disseminated Lupus Erythematosus, Acta radiol. **37**:8, 1952.

21. Miller, H. G., and Daley, R.: Clinical Aspects of Polyarteritis Nodosa, Quart. J. Med. **15**:255, 1946.

22. Elkeles, A., and Glynn, L. E.: Serial Röntgenograms of the Chest in Periarteritis Nodosa as an Aid to Diagnosis, with Notes on the Pathology of Pulmonary Lesions, Brit. J Radiol. **17**:368, 1944.

23. Doub, H. P.; Goodrich, B. E., and Gesh, R., Jr.: The Pulmonary Aspects of Polyarteritis (Periarteritis) Nodosa, Am. J. Roentgenol, to be published.

24. (*a*) Bloom, J., and Rubin, J. H.: Transient Pulmonary Manifestations in Rheumatoid Arthritis, Canad. M. A. J. **63**:355, 1950. (*b*) Ellman, P., and Ball, R. E.: "Rheumatoid Disease" with Joint and Pulmonary Manifestations, Brit. M. J. **2**:816, 1948.

Rheumatic pneumonia differs strikingly from scleroderma in its clinical aspects. The roentgen findings are usually those of vascular congestion or pulmonary edema and do not resemble the changes found in scleroderma.[25]

Differentiation from other diseases causing diffuse interstitial pulmonary fibrosis is obviously difficult, if not impossible. The acute diffuse interstitial fibrosis of the lungs described by Hamman and Rich[26] can be distinguished chiefly by its clinical course, which is rapid, terminating in death in a period of time ranging from three days to several months. The pneumoconioses classically have a nodular rather than a thin linear type of fibrosis, which predominates in the upper outer portion of the lung fields rather than in the bases.

Pulmonary emphysema may be associated with pulmonary fibrosis of either the idiopathic type or that found in association with the pneumoconioses. In none of our cases of pulmonary scleroderma was there a significant degree of emphysema, as determined by roentgenographic criteria. This absence of emphysema in scleroderma may be useful in the roentgenographic differential diagnosis. Additional diagnostic assistance may be obtained by roentgenographic examination of other parts of the body. Characteristic changes in the teeth and bones, soft tissue calcification, and esophageal changes when present offer valuable clues to the presence of scleroderma.

SUMMARY

Five cases of pulmonary scleroderma with similar roentgenographic features are presented.

The roentgen appearance is characterized by a diffuse linear infiltration, more marked in the lower half of the lung fields.

Scleroderma of the lungs may clinically precede the development of cutaneous sclerosis and should be considered in the differential diagnosis of obscure causes of pulmonary fibrosis.

Pulmonary manifestations of other collagen diseases are discussed. When the roentgenographic appearance is correlated with the clinical findings, a more precise diagnosis may be made.

25. Seldin, D. W.; Kaplan, H. S., and Bunting, H.: Rheumatic Pneumonia, Ann. Int. Med. **26**:496, 1947.

26. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of Lungs, Bull. Johns Hopkins Hosp. **74**:177, 1944.

STILBAMIDINE IN TREATMENT OF DISSEMINATED BLASTOMYCOSIS

Report of Two Cases

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PROPAMIDINE, an aromatic diamidine, was shown in 1945 to be effective against Blastomyces dermatitidis in vitro.[1] In 1951, propamadine and stilbamidine were used successfully in the treatment of two cases of disseminated blastomycosis.[2] A subsequent report [3] has shown continued excellent results with the use of stilbamidine.

In support of the evidence cited above we are reporting the results in two cases in confirmation of the value of stilbamidine in the treatment of blastomycosis of the disseminated variety.

REPORT OF CASES

CASE 1.—*First Admission.*—History: J. G. H., a 39-year-old man of Mexican descent, was first admitted to Hines Hospital on Feb. 6, 1951. The diagnosis on admission was right upper lobe pneumonia. He complained of having had hemoptysis since Dec. 28, 1950. The blood was mixed with a white sputum and was present in only small amounts. The patient had been entirely well until that time. He felt feverish. He stated that his normal weight was about 200 lb. (90 kg.) and estimated that he had lost at least 20 lb. (9 kg.). He had received both penicillin and streptomycin injections repeatedly from his family physician before admission to this hospital. He complained of having had night sweats for three consecutive nights the week prior to admission. He had had generalized weakness and a dull aching heaviness in the right upper anterior chest since the onset of the illness. He had never worked in a stone quarry or mine. He had been born in Texas and had lived near Chicago for over 10 years. His occupation during most of that time was as a worker in the steel mills. There had been no known contact with tuberculosis.

Physical Examination: The physical examination at the first admission showed a muscular white man who did not appear acutely ill. He had an occasional cough. Examination of the

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1. Elson, W. O.: The Antibacterial and Fungistatic Properties of Propamidine, J. Infect. Dis. **76**:193-197 (May-June) 1945.

2. Schoenbach, E. B., and others: Systemic Blastomycosis Treated with Stilbamidine, J. A. M. A. **146**:1317-1318 (Aug. 4) 1951.

3. Schoenbach, E. B., and others: The Treatment of Systemic Blastomycosis with Stilbamidine, Ann. Int. Med. **37**:31-48 (July) 1952.

chest showed a moderate increase in the anterior-posterior diameter. The diaphragmatic excursions were normal to percussion bilaterally. There was normal resonance to percussion throughout the chest, with no change in vocal and tactile fremitus. Occasional crepitant rales were heard in the right upper anterior chest. A few small inguinal lymph nodes were palpable bilaterally, but there was no other lymphadenopathy.

Laboratory Data: On first admission the red blood cell count was 4,100,000; the white blood cell count was 15,300 with 95% neutrophiles and 5% lymphocytes. The sedimentation rate was 22 mm. Blood urea nitrogen was 10 mg. per 100 cc. Total protein was 7.5 gm. with albumin 3.5 gm. and globulin 3.8 gm. per 100 cc. Multiple 24-hour sputum specimens were negative for tubercle bacilli on direct smear. A 24-hour sputum specimen was negative on guinea pig inoculation. Blastomycin, coccidiodin, and histoplasmin skin tests were negative. A second strength purified protein derivative tuberculin skin test was 4+. The chest x-ray on admission showed a dense almost homogenous opacity obscuring the upper half of the right hemithorax. On the lateral chest x-ray the density appeared to be primarily posterior. Bronchoscopic culture for acid-fast bacilli was negative. The prothrombin time was 57%. Blood culture was negative. Repeated sputum cultures were negative for pathogenic yeasts and fungi. The white blood cell count remained elevated, as did the sedimentation rate. The sedimentation rate had returned to normal by March 8, 1951. On May 31, 1951, total protein was 6.5 gm., with albumin 3.4 gm. and globulin 3.1 gm. per 100 cc. The white cell count was normal after May 15, 1951. On May 19, 1951, the nonprotein nitrogen was 33.5 mg. per 100 cc. and the icteric index was 5.5. On two occasions Candida albicans was recovered from sputum cultures for fungi.

Course in the Hospital: On admission the patient was immediately started on 300,000 units of penicillin twice daily. This dose was reduced to 300,000 units daily, starting Feb. 15. On Feb. 14, therapy with 500 mg. of aureomycin every six hours was started. Use of aureomycin and penicillin was discontinued on Feb. 19; chloromycetin, 500 mg. every six hours, and dihydrostreptomycin, 1 gm. daily, were started. On March 12, antibiotic therapy was changed to streptomycin 1 gm. twice weekly, and paraaminosalicylic acid, 3 gm. four times a day. Use of paraaminosalicylic acid was stopped on May 10. The patient continued to have a temperature of 99.4 to 100 F. until March 15, and he was thereafter afebrile.

Right thoracotomy was performed on May 16, 1951, because carcinoma had not been ruled out. At the time of surgery the apical and posterior segments of the right upper lobe were completely atelectatic and bound to the chest wall by extremely dense vascular adhesions. The apical portion of the superior segement of the lower lobe was bound also to this inflammatory mass. No normal dissection planes could be followed, owing to the mass of vascular, adherent, tough, inflammatory tissue. Because of the slow resolution of the infiltration the complete upper lobe was removed. The pathological specimen showed that most of the alveoli were replaced by dense fibrous tissue. In the interstitial tissue there were numerous granulomata, which were composed of foreign body giant cells and epithelioid cells. The foreign body giant cells contained a vacuolated material. There was no caseation seen in these granulomata. The pathological diagnosis was chronic fibrosing pneumonitis with foreign body granulomata. The postoperative course was essentially uneventful. Penicillin, 600,000 units and oxytetracycline (Terramycin), 250 mg. every six hours were given for two weeks postoperatively. The patient was discharged from the hospital July 17, 1951, after having gained weight and again showing excellent general health. There were no symptoms referable to the chest, and the physical examination of the lungs showed no abnormality. The chest x-ray at the time of discharge showed no evidence of pulmonary infiltration. Potassium iodide, 15 drops four times a day, was administered from May 29, 1951, until this man's second admission to the hospital.

Second Admission.—History: The patient was seen at follow-up examination Oct. 15, 1951. At that time he complained of a slight nonproductive cough. He had had no fever or hemoptysis. His appetite was good, and he was gaining weight. X-ray of the chest showed no evidence of pulmonary infiltration.

The patient returned to this hospital on May 15, 1952, stating that three weeks prior to admission he had noticed a small pimple on the left lateral aspect of his nose and another in the right scapular area. He scratched these and subsequently noticed increase in size and purulent drainage. This continued until the time of admission, with the lesions gradually increasing in size.

He also complained that two weeks prior to entry his right fifth toe began to itch and he began to notice swelling. This was followed by redness, tenderness, and bluish discoloration accompanied by bloody discharge from the toe. Drainage had continued, and at the time of admission there had been no improvement on treatment by the patient's private physician.

Physical Examination: The patient was seen to be a well developed, moderately thin, white man appearing chronically ill. There was a crusted, soft, purulent, draining mass of the left lateral aspect of the nose measuring 2 by 3 by 1.5 cm. Prostatic examination showed 4+ enlargement of the right lobe of the prostate, with slight tenderness and a questionable area of fluctuation. The back showed a crusted healing ulceration over the right subscapular area, measuring 2 by 3 cm. The right fifth toe was enlarged approximately three times the normal size. The skin was a dusky bluish-red, with an ulceration of the medial aspect of the tip draining seropurulent material. The remainder of the physical examination showed no significant abnormalities.

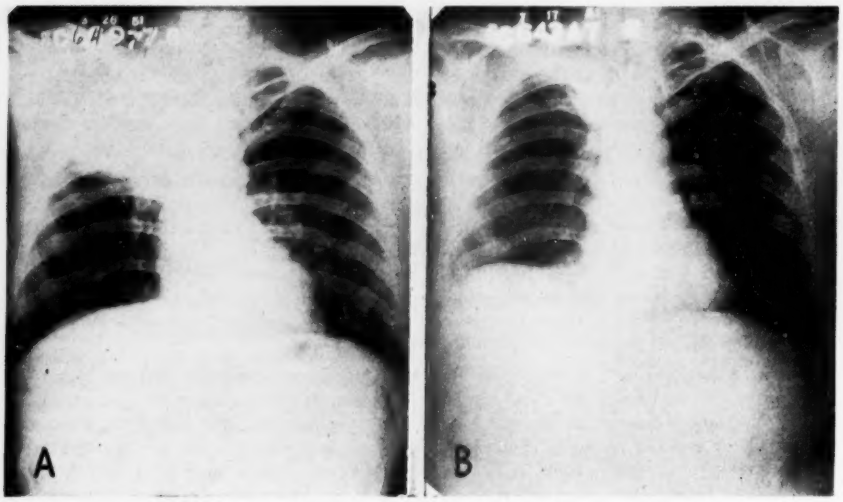

Fig. 1 (Case 1).—*A*, pulmonary lesions prior to treatment; *B*, appearance of chest after lobectomy.

Laboratory Data: The red blood cell count was 4,680,000, with 14 gm. hemoglobin. The white cell count was 11,800, with 70% neutrophiles, 23% lymphocytes, and 7% eosinophiles. Urinalysis showed a trace of albumin initially. Total protein was 7.2 gm., with albumin 3.4 gm. and globulin 3.8 gm. per 100 cc. Sedimentation rate was 22 mm. Thymol turbidity test showed 19 units, alkaline phosphatase 3.2 mg. per 100 cc. and cephalin flocculation 2+ in 24 hours and 4 plus in 48 hours. Biopsy from the nasal lesion showed occasional discrete doubly refractile spherical bodies in the inflammatory areas. These bodies had a central nuclear mass and ranged from 20 to 40μ in diameter. They were identified as B. dermatitidis organisms. This organism was also found on review of the lung sections removed during the first admission. The prostate was not enlarged but was slightly tender; no secretion was obtained after repeated attempts. X-ray study showed soft tissue swelling of the fifth toe of the right foot, with moderate osteoporosis of all the phalanges. There was no evidence of bone destruction. Chest x-ray disclosed elevation of the right diaphragm; there was no pulmonary infiltration.

Course in the Hospital: On May 16 a culture of the nasal lesion for fungi showed budding yeast cells. Blood cultures were also taken on this date. The patient received moist hot compresses to the nose and right foot plus antibiotics until May 20, 1952, at which time the dressings were changed from wet to dry dressings. During this period the nasal lesion showed marked

improvement, with a decrease in size and in purulent drainage. The right fifth toe also showed considerable improvement, but swelling and tenderness persisted. Antibiotics were continued, and the patient was started on therapy with potassium iodide. On June 12, 1952, the patient was started on stilbamidine therapy. This was given intravenously; the dosage was as follows: 50 mg. for the first two days, 100 mg. the next two days, and 150 mg. daily for a total of 18 days. During this time neomycin sulfate was used topically on the involved area. The proliferative cutaneous lesions of blastomycosis during this period resolved remarkably, so that at the end of the course of therapy erythema was the only remaining evidence of the lesions. The right fifth toe had healed completely. The patient was discharged and is being examined at frequent intervals for evidence of further involvement.

Fig. 2 (Case 1).—*A*, nasal lesions prior to treatment with stilbamidine; *B*, appearance of patient on Feb. 5, 1953, showing the complete healing of the nasal lesion.

Summary.—This 39-year-old man was admitted with a diagnosis of right upper lobe pneumonia and was treated with antibiotics and potassium iodide from Feb. 6, 1951, until May 16, 1951. There was gradual resolution of the right upper lobe infiltration. Because of the slow resolution lobectomy was performed. The pathological diagnosis was chronic fibrosing pneumonitis with foreign body granulomata.

The patient was readmitted 11 months after discharge because of skin lesions of the nose and right scapula. Biopsy of these lesions disclosed B. dermatitidis. This organism was also found upon review of the microscopic sections of the lung, made during the first admission. The dermatological lesions remained stationary with management and antibiotics, iodides, and local moist compresses. The patient was consequently treated with a total dose of 2.4 gm. of stilbamidine intravenously, and the lesions rapidly cleared. Potassium iodide therapy is being continued.

On the second admission the chest x-ray disclosed no abnormality. The microscopic slides of the lung were reviewed, and B. dermatitidis organisms were found

in the giant cells. Liver function tests showed parenchymal damage, for which no specific cause could be found. There were no other signs of the disseminated blastomycosis.

This case exemplifies the chronic and elusive nature of this disease. Apparently the patient has been benefited by stilbamidine therapy and has shown no sign of toxic manifestations from the drug.

Reexamination.—The patient reported for reexamination on Feb. 5, 1953, approximately three months after discharge. He had gained approximately 90 lb. (40.5 kg.) since being placed on stilbamidine therapy. The lesion of the nose was smoothly healed, and the lesions of the right scapular region were well healed. The patient's general sense of well-being and health were excellent. He is active and working. There has been no fever. He stated that during this interval he had noted numbness and stiffness of the face and forehead and a twitching of his eyelids. There was no pain or puritis. He stated that on several occasions cigarettes dropped from his lips without his being aware that this was occurring. He stated that these symptoms were rapidly improved.

CASE 2.—*History.*—The patient, a 49-year-old man, had been working as a meat salesman since 1943, a job entailing considerable handling of meat. He had lost 27 lb. (12.2 k.) since the onset of the present illness. He was admitted to this hospital on May 30, 1952. He had been well up until March 8, 1952. On that day he noticed swelling and soreness of the dorsum of his right foot. He was treated with large doses of penicillin and had been given cortisone (Cortone). He was seen by another physician, in Raleigh, Ill., on March 31, 1952, because the swelling of his right foot had not responded to treatment. X-rays of the foot revealed partial destruction of the third, fourth, and fifth metatarsal and the cuboid bones. The diagnosis of osteomyelitis was made. An attempt was made surgically to remove all the diseased tissue. No cultures were made.

Three weeks later x-ray studies of the foot were again made and it was found that the bony destruction had progressed. A below-knee amputation was performed, and the dissected foot showed large areas of necrosis, with a number of abscesses. The pathological report indicated that the disease was blastomycosis. The patient was x-rayed, and it was stated that there was involvement of the lungs. In late May of 1952, he began to have difficulty in passing urine. On May 25, 1952, complete urinary retention developed. The patient was transferred to Hines Hospital on May 30, 1952. At the time of admission he gave no history of urinary difficulty prior to this episode. There had been no uretheral discharge. He had always had a good urinary stream until one month prior to admission, when he began to notice that his urinary stream was weaker.

Physical Examination.—At the time of admission the patient weighed 126 lb. (56.7 kg.). Blood pressure was 128/78, pulse rate 92 and regular. He appeared chronically ill. There was a retention catheter in his bladder, which was draining clear urine. There was a below-knee amputation of the right leg, with a small granulation area still present on the stump. The prostate was Grade 1 to 2 enlarged, firm, and slightly tender. There was deformity of the left hand, a result of an accident in 1943.

Laboratory Data.—The red blood cell count was 3,910,000, hemoglobin 11.5 gm., and white cell count 15,200. Routine urine studies disclosed 20 white blood cells and 2 red blood cells per high-power focus. Nonprotein nitrogen was 28.2 mg. per 100 cc. The chest x-rays showed a coarse granulated type of infiltration in the upper areas of both lung fields and increased markings in the lower half of the right lung field. X-ray of the lumbosacral spine revealed narrowing of the fifth lumbar interspace, with hypertrophic changes of the contiguous anterior and posterior borders consistent with degenerative arthritis. X-rays of the stump of the right leg revealed no evidence of osteomyelitis. An intravenous pyelogram showed no definite abnormality. X-ray studies of the ribs showed no abnormality. The urine was negative for Bence Jones protein. There was no growth from pus aspirated from a lesion of the left heel. The sedimentation rate was 27 mm. One routine urinalysis, on June 10, showed a fungus resembling a blastomycosis organism; many other specimens of urine were negative for yeasts and fungi. The white blood cell count was consistently elevated, around 13,000. Thymol turbidity was 6 units. Total protein was 6.4 gm., albumin 3.2 gm., and globulin 3.2 gm. per 100 cc. Alkaline phosphatase was 4.0 mg.

per 100 cc. The cephalin flocculation test was negative. A sulfobromophthalein test showed no retention. Repeated sputum specimens were negative for fungi. By Aug. 28, 1952, the red blood cell count was 4,400,000. Hemoglobin was 14 gm. The white cell count was 12,000, with 70% neutrophiles, 27% lymphocytes, and 3% eosinophiles. The total protein was 5.9 gm.; albumin was 3.7 and globulin 3.2 gm. per 100 cc. Biopsy of a skin lesion of the right thigh showed many organisms of blastomycosis dermatitidis.

Course in the Hospital.—The patient was admitted to the genitourinary service at this hospital. At the time of admission a smear of the prostatic secretion was made, which showed doubly refractile organisms, which did not grow on culture. The prostate was enlarged, 1 to 2+, firm, and slightly tender. Cystoscopy disclosed early lateral lobe hypertrophy and inflammation of the prostatic urethra. There did not appear to be sufficient benign prostatic hypertrophy to cause an acute retention The Foley catheter was removed on June 12, and subsequently the patient has been able to void without difficulty On June 16 the patient began

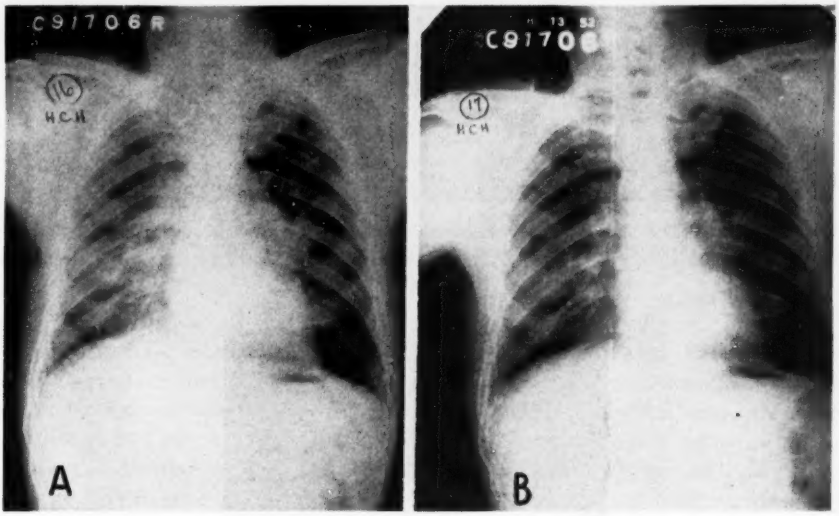

Fig. 3 (Case 2).—*A*, diffuse infiltrative lesions of the lungs before treatment; *B*, x-ray appearance of chest after stilbamidine therapy.

to have a moderate cough, with pain in his right chest. His temperature rose to 102 F., whereas prior to this time the temperature had been normal. A small plantar subcutaneous abscess of the left foot developed. He was consequently transferred to the isolation ward. The plantar abscess of the left foot was 1 inch (2.5 cm.) in diameter; thick light-greenish pus was obtained and a specimen taken for smear and culture. The patient continued febrile. Moist crepitant rales developed in the right lower lung fields. At the time of admission medication had been started with sulfisoxazole (Gantrisin), 1 gm. four times a day, and shortly thereafter penicillin, 300,000 units, was given twice daily. On June 13 therapy with oxytetracycline (Terramycin), 250 mg. four times a day, was started. The sulfisoxazole and penicillin were stopped on June 16. Use of saturated solution of potassium iodide, 10 drops four times a day, was started on June 16. This was increased to 15 drops four times a day June 20. On June 25, chloromycetin, 250 mg. four times a day, was initiated and the oxytetracycline was discontinued, as was the potassium iodide. The temperature returned to normal two days after chloromycetin therapy was started and remained normal, except for an occasional spike, until July 26. At that time multiple skin lesions and subcutaneous abscesses had begun to develop. He generally did not feel well and was not eating. He was nauseated and had a moderate cough which was unproductive. The temperature was elevated, between 101 and 102 F. On July 28

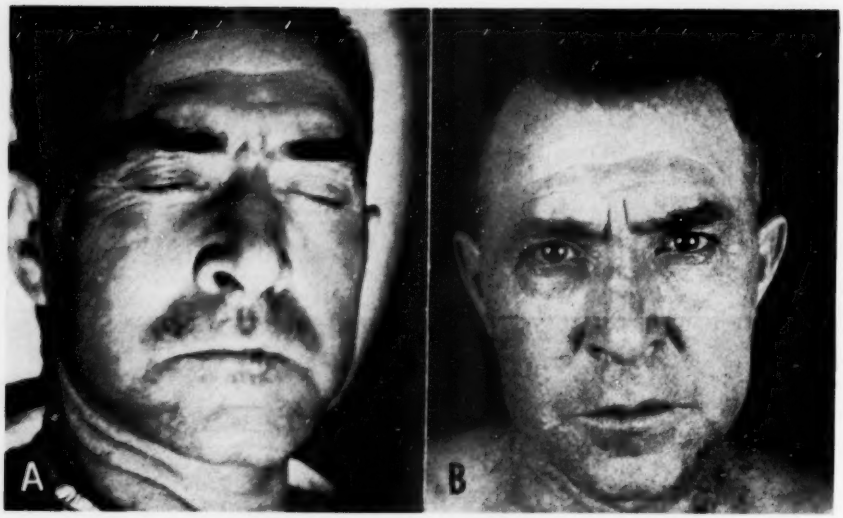

Fig. 4 (Case 2).—*A*, appearance of lesion on lower lip prior to treatment; *B*, appearance of patient on Feb. 5, 1953, showing the complete healing of lower lip.

Fig. 5 (Case 2).—Lesions of osteomyelitis of the foot prior to amputation.

chloromycetin was stopped and treatment with stilbamidine was initiated. The patient received 50 mg. of stilbamidine intravenously the first day, 75 mg. the second day, 100 mg. the next two days, and 150 mg. daily thereafter for a total of 16 days. The temperature within three days had returned to normal and was normal thereafter. The patient soon noticed great improvement in his sense of well-being; his appetite improved and since that time he has desired double servings of food at least twice a day. His weight increased from 119 to 137 lb. (55.4 to 61.7 kg.), his normal weight being around 155 lb. (69.8 kg.). The skin lesions and lesion of his lower lip gradually disappeared. He has continued on an active physical therapy program. On Aug. 14 he began to complain of difficulty in urination, both of frequency and of nocturia. Culture of a prostatic smear showed the organism B. dermatitidis. Because of this it was decided that at least one more course of stilbamidine was indicated and the patient received another 12-day course of stilbamidine, 150 mg. daily in 250 cc. of isotonic sodium chloride by intravenous drip. The total amount of stilbamidine administered was 3.92 gm. There have been no signs of neuropathy or any other reaction to the drug. Renal and liver function studies have shown no abnormalities, and there have been no further skin or subcutaneous lesions. The chest x-ray has shown a decrease in the amount of diffuse pulmonary infiltration.

Summary.—This 49-year-old white man, a meat handler, acquired osteomyelitis of the right foot, which progressed so rapidly that a below-knee amputation was performed about one month after the onset of symptoms. The pathological study disclosed B. dermatitidis. One month later complete urinary retention occurred and the patient entered Hines Hospital May 30, 1952. Organisms of B. dermatitidis were found in the initial prostatic smear. Chest x-ray showed a coarse granular type of infiltration bilaterally; the organisms were not recovered in the sputum.

This patient shortly thereafter became febrile and developed multiple cutaneous abscesses. His symptoms subsided with chloromycetin therapy only to recur despite continuance of this drug. Fairly suddenly a high fever, anorexia, multiple skin lesions, and subcutaneous abscesses developed. The patient then received a course of 2.12 gm. of stilbamidine, which was followed by subsidence of all symptoms and a surprising weight gain. The skin lesions cleared gradually, and four weeks after treatment no lesions were apparent. Chest x-ray showed improvement.

Three weeks after discontinuance of treatment symptoms of urinary retention developed. At this time smear and culture were positive for B. dermatitidis. There was no fever or generalized symptoms at this time, but the patient was given another course of stilbamidine (total 1.8 gm.). It is our intention to follow this patient closely, as the organisms may still be present. No signs of drug toxicity have developed. Liver and renal function remain unimpaired.

Reexamination.—Follow-up on Feb. 6, 1953, showed the patient to be in good physical condition. He had gained approximately 40 lb. (18 kg.). The lesions on the lip and the multiple subcutaneous sinuses were well healed. A prostatic smear was negative for blastomycosis. The patient was feeling well and strong at this time. This patient also states that he has had numbness and tingling over the face and forehead during the past few months. These symptoms had nearly disappeared at the time of examination.

COMMENT

These two cases of proved disseminated blastomycosis have, to date, shown satisfying results from stilbamidine therapy. A much longer period of follow-up is essential before a permanent cure can be assumed.

The previous clinical experience with respect to the treatment of this disease has been most unsatisfactory.[4] If one reviews the literature one will find that various remedies used alone or in combination did not alter the pessimistic outlook to any appreciable degree. Chances of recovery at best were regarded as very unlikely. Considerable question has been raised as to the advantage or disadvantage of some procedures. This is particularly true of the use of iodides for the systemic type of the disease.

It has been indeed gratifying to observe the results of stilbamidine therapy herein recorded in a disease in which the clinical outlook has been so bleak. While it is not justifiable to assume that stilbamidine is specifically curative, our experience, along with other reports, is very stimulating and encouraging.

Both penicillin and streptomycin have been reported ineffective. In these cases aureomycin, chloromycetin, and oxytetracycline (Terramycin) were used without results. Paraaminosalicyclic acid in combination with dihydrostreptomycin was likewise uneffective.

With patients who have disease of the liver or kidneys, great caution must be used, and the drug is probably contraindicated if such disease is advanced.[5] Also, the patient should remain reclining for several hours after administration because of the possibility of acute hypotensive reaction.[6] Neuropathy including a peculiar predisposition for involvement of the fifth nerve has been described by many observers.

Sen Gupta [7] reported that 17 of 104 patients treated with diamidine showed evidence of neuropathy. Snapper [8] has also emphasized the constant occurrence of neuropathy if sufficient dosage is used. Symptoms of fifth nerve neuritis may be severe and persist for years. Very small doses may cause neuropathy, but in general the severity seems to parallel the dose. Snapper is of the opinion that exposure to sunlight changes the stilbamidine deposited in the nerves into a toxic form. He also reports that 2-hydroxystilbamidine is comparatively little affected by sunlight, hence neuropathy does not occur in comparable dosage. Thus, prolonged protection from sunlight might greatly decrease the incidence of neuropathy.

While the neural involvement in these two patients was mild, it serves to emphasize the occurrence of this effect even though very moderate dosage has been used.

It must be kept in mind that stilbamidine possesses potential toxicity, and careful watch for such signs is indicated. We have been pleased that the total dosage used for these patients mentioned in the literature was less than the 4 to 6

4. Martin, D. S., and Smith, D. T.: Blastomycosis (American Blastomycosis, Gilchrist's Disease): Report of 13 New Cases, Am. Rev. Tuberc. **39**:488-515 (April) 1939.

5. Arai, H., and Snapper, I.: The Influence of Stilbamidine Upon Kidney Function, Liver Function, and Peripheral Blood in Multiple Myeloma: Neurologic Sequelae of Stilbamidine Therapy, New York J. Med. **47**:1867-1874 (Sept. 1) 1947.

6. Kirk, R., and Henry, A. J.: Observation on the Toxicity of Stilbamidine, Ann. Trop. Med. **38**:99-118 (Sept.) 1944.

7. Sen Gupta, P. C.: Observations on Neuropathic Sequel of Diamidino-Stilbene Therapy in Kala-Azar, Indian M. Gaz. **78**:537-543 (Nov.) 1943.

8. Snapper, I.; Schneid, B.; McVay, L., and Lieben, F.: Pharmacology and Therapeutic Value of Diamidine Derivatives—Particularly of 2-Hydroxystilbamidine, Tr. New York Acad. Sc. **14**:269-271 (May) 1952.

gm. Lower dosage may be effective in decreasing or eliminating both early and late toxic complications. Careful attention was given to administering the drug immediately after mixing, and no toxic signs were observed in our patients.

It is not yet known what the long-term success of this treatment will be. This is particularly true of skeletal lesions. It may be that repeated courses of treatment will be necessary at intervals of several months in order to prevent relapse of the disease. Hydroxystilbamidine, with its low toxicity level, will be of great importance if such treatment is necessary.

The recent observation of Curtis and Harrell,[9] that diethylstilbestrol and methyl testosterone show an inhibiting effect in vitro on Blastomyces dermatitidis, is of interest. Their report of satisfactory results in the treatment with diethylstilbestrol of two patients with cutaneous blastomycosis increases the importance of this observation with respect to future investigation.

SUMMARY

Two patients with disseminated blastomycosis were treated with stilbamidine. The results to date have been good. There was definite evidence of toxic neuropathy involving the fifth nerve in both patients. This was mild and insignificant in view of the clinical improvement.

9. Curtis, A. C., and Harrell, E. R.: Use of 2 Stilbene Derivatives (Diethylstilbestrol and Stilbamidine) in Treatment of Blastomycosis, Arch. Dermat. & Syph. **66**:676-690 (Dec.) 1952.

Progress in Internal Medicine

THE THREE SUBTYPES OF PITUITARY ADRENOCORTICOTROPIN

Basic Physiology, Quantitative Human Pharmacology, and Medical Usefulness of ACTH-Corticotropin ("Corticotropin, Crude," "U.S.P. Corticotropin"), ACTX-Corticotropin ("Corticotropin, Purified," "Corticotropin A," "Type I Purified ACTH") and ACTIDE-Corticotropin ("Corticotropin B")

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CRUDE extracts cannot be medically useful until a satisfactory bioassay method permits their potency to be described in quantitative units which parallel the clinical potency in patients. Bioassay methods for corticotropin were unsatisfactory until the adrenal ascorbic acid depletion method was introduced by Sayers, Sayers, and Woodbury, in 1947.[1] Using rats which had been hypophysectomized to remove their source of endogenous corticotropin, these investigators demonstrated a linear relationship between the logarithm of the dosage of intravenously administered corticotropin and the resulting decrease in adrenal ascorbic acid concentration. An acceptable assay permitted standards for corticotropin to be established. The first was the Armour "milligram," later superseded by the International Unit and the U. S. P. unit; all are essentially identical and interchangeable.

Until quite recently, the clinical activity of intramuscularly administered corticotropins appeared to parallel potency determined by the ascorbic acid depletion bioassay, in which the corticotropins are administered intravenously. Attempts to purify corticotropin led to two new materials, which, when given intramuscularly, exhibit activity far different from that anticipated from bioassay of intravenously administered corticotropin. It is now actually necessary to distinguish three

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Brief reports of portions of these findings have appeared elsewhere (Wolfson, W. Q., and Robinson, W. D.: Fed. Proc. **11**:623, 1952. Wolfson, W. Q., and Fajans, S. S.: New England J. Med. **246**:1000, 1952).

These studies were performed during Dr. Wolfson's appointment as Research Associate. Rackham Arthritis Research Unit. Dr. Wolfson is now Research Associate, Department of Internal Medicine, Wayne University College of Medicine and Armour Fellow in Quantitative Human Pharmacology, 1953-1954.

1. (*a*) Sayers, M. A.; Sayers, G., and Woodbury, L. A.: The Assay of Adrenocorticotrophic Hormone by the Adrenal Ascorbic Acid-Depletion Method, Endocrinology **42**:379, 1948. (*b*) Astwood, E. B.; Raben, M. S., and Payne, R. W.: Chemistry of Corticotropin, in Recent Progress in Hormone Research: Proceedings of the Laurentian Hormone Conference, edited by G. Pincus, New York, Academic Press, Inc., 1952, Vol. 7, pp. 1-58.

corticotropin subtypes: (1) "corticotropin, crude," the familiar ACTH-corticotropin, which has been generally available and is best exemplified by the U. S. P. corticotropin standard; (2) "corticotropin, purified," also known as "high-potency corticotropin" and designated ACTX-corticotropin in this report, and (3) ACTIDE-corticotropin, the highly purified material isolated from peptic hydrolysates of crude corticotropin.

ACTIDE-Corticotropin ("Corticotropin B"), a Corticotropin Subtype with a Low Ratio of Extravascular to Intravenous Activity.—Belief in the existence of a small molecule with corticotropic activity and efforts to isolate the hypothetical "ACTH-peptide" were encouraged by the ultrafiltrability of corticotropin under suitable circumstances and by the persistence of activity after peptic hydrolysis.[2] Li [3] suggested that ACTIDE denotes the corticotropic substance in peptic hydrolysates of crude corticotropin.[4] At The Armour Laboratories, fractions more than 50 times as active per milligram as the reference standard [2c,d] were prepared from corticotropin hydrolysates.

Careful clinical studies were carried out by Forsham, Renold, and Lesh,[5] using an ACTIDE-corticotropin which had a potency of 103 U. S. P. units per milligram. When administered to man by intravenous infusion, the metabolic changes noted were consistent with the animal bioassay values. However, when the ACTIDE-corticotropin was given intramuscularly, the metabolic alterations observed were only about one-fourth as intense as expected. A few preliminary studies in this laboratory with similar materials also suggested that their intramuscular effectiveness was considerably less than anticipated.[6] Because it already was generally appreciated that most of the crude ACTH-corticotropin given subcutaneously or intramuscularly was inactivated or destroyed in the extravascular tissues,[7] Forsham,

2. (*a*) Geschwind, I. I.; Hess, G. P.; Condliffe, P. G., and Williams, B. S.: Preparation of Nonprotein Fractions Possessing Adrenocorticotrophic Activity from Sheep ACTH Protein, Science **111**:625, 1950. (*b*) Dedman, M. L.; Farmer, T. H.; Morris, P., and Morris, C. J. O. R.: Purification of the Pituitary Adrenocorticotrophic Hormone, in Recent Progress in Hormone Research: Proceedings of the Laurentian Hormone Conference, edited by G. Pincus, New York, Academic Press, Inc., 1952, Vol. 7, pp. 59-74. (*c*) Lesh, J. B., and others: Studies on Pituitary Adrenocorticotropin, Science **112**:43, 1950. (*d*) White, W. F.; Fierce, W. L., and Lesh, J. B.: Studies on Pituitary Adrenocorticotropin: Paper Chromatography of Pepsin Treated Materials, Proc. Soc. Exper. Biol. & Med. **78**:616, 1951.

3. Li, C. H.: The Present Status of the Chemistry of ACTH, in Transactions of the Second Conference on the Adrenal Cortex, edited by E. P. Ralli, New York, Josiah Macy, Jr., Foundation, 1950, pp. 11-47.

4. Use of ACTIDE in this report should not be considered as indicating acceptance of Li's hypothesis that a relatively small peptide is responsible for the corticotropic activity of peptic hydrolysates of crude corticotropin.

5. Forsham, P. H.; Renold, A., and Lesh, J. B.: Metabolic Effects of Small Molecular ACTH: A Preliminary Report, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 1: Research.

6. Unpublished data.

7. (*a*) Gordon, E. S.; Kelsey C., and Meyer, E. S.: Adrenal Stimulation by Intravenous ACTH, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2: Therapeutics. (*b*) Renold, A. E.; Forsham, P. H.; Maisterrena, J., and Thorn, G. W.: Intravenously Administered ACTH: A Preliminary Report, New England J. Med. **244**:796, 1951. (*c*) Mandel, W., and others: Intravenous Use of Pituitary Adrenocorticotrophic Hormone (ACTH): Report on Its Administration in 25 Patients, J. A. M. A. **146**:546, 1951. (*d*) McIntosh, H. W., and Holmes,

(Footnote continued on next page)

Renold, and Lesh suspected that ACTIDE-corticotropin was even more susceptible to extravascular inactivation than was the crude ACTH-corticotropin from which it had been prepared. Other clinical studies employing ACTIDE-corticotropins do not permit a comparable comparison of potency.[8]

A recent study by Ingle and Li suggests that the marked susceptibility of ACTIDE-corticotropin to extravascular inactivation is not a species-specific characteristic.[9] Ingle and Li employed an ACTIDE-corticotropin which when given by continuous intravenous infusion was approximately twice as effective per milligram in inducing hypercorticoidism in rats as their standard crude ACTH-corticotropin.[10] However, in rats given the same materials by continuous subcutaneous infusion the ACTIDE appeared only about half as effective as an equal weight of ACTH in inducing hypercorticoidism.[11] Thus Ingle and Li's results indicated that the extravascular effectiveness of ACTIDE, per unit of intravenous activity, was only approximately 25% of the extravascular effectiveness of ACTH in the rat.

Because of its high degree of susceptibility to extravascular inactivation ACTIDE-corticotropin is not clinically promising and therefore has received considerably less study than the other subtypes. It continues to be important as a possible approach to the fundamental chemistry of corticotropins.

ACTX-Corticotropin ("Purified Corticotropin," "High-Potency Corticotropin," "Corticotropin A,[1] Type I. Purified ACTH of Fisher and Thompson[11a]), a Corticotropin Subtype with a High Ratio of Extravascular to Intravenous Activity.—In an important series of studies, Astwood and his associates obtained a 25- to 40-fold purification of corticotropin by relatively simple procedures, notably chromatographic fractionation of crude corticotropin (glacial acetic acid process) on columns of oxidized cellulose.[12] In clinical studies[13] the intramuscular effectiveness of ACTX-corticotropin eluted from the columns was compared with that of the original crude ACTH-corticotropin. Both were given intramuscularly in

C. B.: The Intravenous Use of ACTH, Canad. M. A. J. **65**:33, 1951. (*e*) Jelliffe, A. M.; Stewart, P. B., and Beaumont, G. E.: ACTH by Intravenous Infusion: Preliminary Communication, Lancet **1**:1260, 1951. (*f*) Renold, A. E.; Jenkins, D.; Forsham, P. H., and Thorn, G. W.: The Use of Intravenous ACTH: A Study in Quantitative Adrenocortical Stimulation, J. Clin. Endocrinol. **12**:763, 1952.

8. Luft, R.; Sjögren, B., and Li, C. H.: Results of Administration of Adrenocorticotrophically Active Peptides (ACTH Peptides) to a Patient Suffering from Rheumatoid Arthritis, Acta endocrinol. **3**:299, 1949. Kinsell, L. W., and others: Metabolic Effects of a Peptide Mixture Derived from ACTH (Li) in Comparison with Those Resulting from Whole ACTH Administration in a Human Subject, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 70. Brink, N. G.; Meisinger, M. A. P., and Folkers, K.: The Activity of a Hydrolysate of Adrenocorticotrophic Hormone in Rheumatoid Arthritis, J. Am. Chem. Soc. **72**:1040, 1950.

9. Ingle, D. J., and Li, C. H.: Comparison of Biologic Effects of ACTH Protein and ACTH Peptide Given by Continuous Injection, Proc. Soc. Exper. Biol. & Med. **79**:128, 1952.

10. Ingle, D. J.; Prestrud, M., and Li, C. H.: Effects of Administering Adrenocorticotrophic Hormone by Continuous Injection to Normal Rats, Am. J. Physiol. **166**:165, 1951.

11. Payne, R. W.; Raben, M. S., and Astwood, E. B.: Extraction and Purification of Corticotropin, J. Biol. Chem. **187**:719, 1950.

11a. Fisher, J. D., and Thompson, R. E.: Correlation of Preparative History and Method of Assay of Corticotropin with Clinical Potency, Endocrinology **52**:496, 1953.

12. Astwood, E. B.; Raben, M. S.; Payne, R. W., and Grady, A. B.: Purification of Corticotropin with Oxycellulose, J. Am. Chem. Soc. **73**:2699, 1951. Astwood,[11b] Payne.[11]

13. Raben, M. S.; Rosenberg, I. N.; Westermeyer, V. W., and Astwood, E. B.: Enhanced Clinical Effectiveness of Purified Corticotropin, J. A. M. A. **148**:844, 1952.

aqueous solutions; the total daily dose was divided into three parts and administered every 8 hours. Each U. S. P. unit of the ACTX-corticotropin produced therapeutic effects which, on the average, equaled those produced by 1.9 units of the ACTH-corticotropin. This initial impression of the high intramuscular effectiveness of ACTX-corticotropin per U. S. P. unit has been fully confirmed.[14]

Like the low extravascular effectiveness of ACTIDE-corticotropin, the high extravascular effectiveness of ACTX-corticotropin does not appear to be species-specific. Chart I summarizes an experiment in which Fisher and Thompson [15] administered roughly equal unitages (established by intravenous assay) of ACTH and ACTX to rats by subcutaneous injection. The much greater depression of adrenal ascorbic acid seen in the ACTX-treated rats indicates that in this species, as in man, one U. S. P. unit of ACTX has a subcutaneous effectiveness far greater than that of one U. S. P. unit of ACTH.

By definition, equal unitages of ACTX and ACTH given intravenously to rats must produce identical effects, since unitage is actually established by intravenous rat bioassay. According to the data of Forsham, Renold, and Lesh [5] intravenous intracenous infusions of equal unitages of ACTIDE and ACTH produce approximately identical effects in man.[5] Renold, Jenkins, Forsham, and Thorn [7f] find a similar identity of effect when equal unitages of ACTX and ACTH are given by intravenous infusion. Indeed, when an equal number of U. S. P. units is given intravenously to man, pork ACTH, beef ACTH, sheep ACTH, pork ACTX, and beef ACTX [16] produce identical increases in 17-ketosteroid excretion.

The high effectiveness of ACTX-corticotropin given intramuscularly seems to result from a low susceptibility to extravascular inactivation. Less than 50% of the intramuscularly administered ACTX undergoes extravascular inactivation (Table 4). ACTX-corticotropin is practically important because corticotropin is most often given intramuscularly and because the relatively inexpensive conversion of crude ACTH-corticotropin to high-potency ACTX-corticotropin approximately trebles the intramuscular corticotropic activity obtainable from the starting material. A by-product of this purification is a hormone concentrate which provides an excellent source of growth hormone and certain other pituitary principles.[17] The introduction of ACTX-corticotropin has already reduced the cost of intramuscular treatment with corticotropin to approximately 40% of that obtaining in early 1952. ACTX also has not induced the specific refractoriness to intramuscularly adminis-

14. (*a*) Wolfson, W. Q., and Robinson, W. D.: Corticotropin Preparations Which, when Given Intramuscularly, Exhibit Human Activity Several Times That Anticipated from Animal Bioassay, Fed. Proc. **11**:623, 1952. (*b*) Wolfson, W. Q., and Fajans, S. S.: A Comparison of the Duration of Action of Various Long-Acting ACTH Preparations in Human Subjects, New England J. Med. **246**:1000, 1952. (*c*) Thorn, G. W., and others, in Proceedings of the Third Clinical ACTH Conference, Chicago, The Armour Laboratories, 1952.

15. (*a*) Fisher, J. D., and Thompson, R. E.: Correlation of Preparative History and Method of Assay of Corticotropin with Clinical Potency, Endocrinology **52**:496, 1953. (*b*) Wolfson, W. Q., and Cohn, C.: Rapid Micromethods for the Analytic Fractionation of Serum Proteins, Ann Arbor, Mich., The Overbeck Company, 1952. (*c*) Chattaway, F. W.: Estimation of Histidine in Urine and Its Excretion by Normal and Pregnant Women, Biochem. J. **41**:226, 1947.

16. Jenkins, D.: Personal communication to the author.

17. Raben, M. S., and Westermeyer, V. W.: Recovery of Growth Hormone in Purification of Corticotropin, Proc. Soc. Exper. Biol. & Med. **78**:550, 1951.

tered ACTH which develops in 8% or more of patients who have received two or more courses of treatment with crude ACTH-corticotropin.[7f] Astwood and others have reported that patients with induced intramuscular refractoriness to intramuscular ACTH-corticotropin usually continue to respond normally to intramuscular ACTX.[18]

The Distinction Between Corticotropin Subtypes and Qualitatively Different Corticotropins.—Differentiation of ACTH-corticotropin, ACTIDE-corticotropin, and ACTX-corticotropin as subtypes of corticotropin should not lead them to be considered qualitatively different corticotropins. Whatever fraction of each reaches the adrenal cortex appears to evoke an identical ratio of clinical, metabolic, hematologic, and therapeutic activities, except in one area, discussed more fully below. ACTH, ACTIDE, and ACTX are different not in the pattern of adrenal response evoked but in their interactions with tissues other than the adrenal.

Recent studies have established the existence of a pituitary factor which regulates adrenal function but which differs from all three subtypes of adrenocortico-

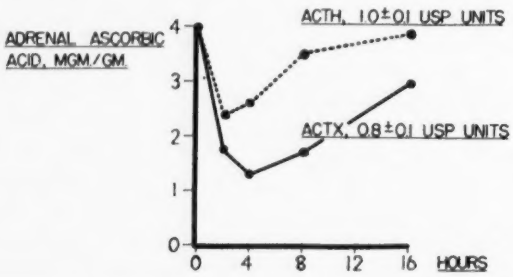


Chart 1.—Comparison of potency of approximately equal unitages (established by intravenous assay) of ACTH and ACTX given extravascularly to rats. Each value is the average of values from four rats. ACTH and ACTX were given subcutaneously in 0.5 ml. of 16% gelatin. (From J. D. Fisher and R. E. Thompson, to be published.)

18. Astwood, E. B., in Proceedings of the Third Clinical ACTH Conference, Chicago, The Armour Laboratories, 1952. Renold.[7f] Two findings are required to establish the existence of the specific intramuscular refractoriness to a particular corticotropin preparation. 1. The patient ceases to respond to intramuscular administration of a daily dosage three times as large as that which originally gave good responses. 2. When 20 U. S. P. units of the identical preparation are given intravenously in a single 8-hour infusion, a good response is obtained. The following recent experience illustrates a different type of unresponsiveness, which is deceptively similar. After more than one year of good control, high grade refractoriness to ACTX developed in a young man with chronic uveitis due to sarcoidosis. He was hospitalized for study. On the first 11 hospital days he received 20 U. S. P. units of gelatin-ACTX intramuscularly every six hours, or the equivalent of 480 units of aqueous crude ACTH per day. On the 12th hospital day, PAWF (pituitary adrenal weight factor, Victory) was added in a dosage of 20 mg. every six hours. Both the ACTX and the PAWF were porcine in origin. Within 48 hours after beginning PAWF, he became moon faced and plethoric, and an extraordinarily extensive acne developed. Because of rapidly increasing responsiveness, it was possible to discharge him under control with 10 U. S. P. units of ACTX and 10 mg. of PAWF daily on the 20th hospital day. We have also seen probable resistance to ACTX develop apparently because of sensitivity to the suspending menstruum in one patient. These two patients did become unresponsive to ACTX, but neither had the type of disturbance designated as specific intramuscular unresponsiveness.

tropin in the following respects: It neither causes an acute fall in adrenal ascorbic acid nor an acute increase in the rate of corticoid secretion but does maintain adrenal weight, ascorbic acid, and cholesterol after hypophysectomy. This factor has variously been termed AWF (adrenal weight factor), PAWF (pituitary adrenal weight factor), and EAPE (equine anterior pituitary extract). Studies of Forsham and Liddle suggest that its administration to man often leads to increased sensitivity of the adrenal cortex to stimulation by corticotropin given subsequently. Our experience with its effect in a young man who had become refractory to ACTX is summarized in a later footnote and tends to support the views of Forsham and Liddle. However, PAWF should be regarded as an entirely different hormone of the pituitary and not as a corticotropin subtype. Corticotropin should be reserved as the designation for the pituitary hormone which induces an immediate increase in the rate at which corticoid hormones are secreted by the adrenal gland in a hypophysectomized animal or in an in vitro perfusion system. So far, all but one corticotropin preparation has also caused an acute decrease in adrenal ascorbic acid concentration. PAWF will not be considered in the present report.

Scope of the Present Report.—In this report there will be described techniques by which the comparative intramuscular effectiveness of ACTX and ACTH were established in man. Studies relating to possible qualitative differences between these subtypes will be described. The parallelism between human extravascular bioassay and animal extravascular bioassay will be documented. Possible application of the findings to tests of adrenal cortex function and to choice of optimum dosage schedules for corticotropin administration will be indicated.

SUBJECTS AND METHODS

Over 500 normal adults and patients participated in assay or therapeutic studies. The normal adults included physicians and laboratory technicians working at University Hospital and also nondiabetic relatives of patients with diabetes mellitus, studied through the cooperation of Dr. S. S. Fajans. Patients included mild diabetics, also studied through Dr. Fajans' help; patients with corticoid-sensitive acute or chronic ocular disorders, studied in cooperation with Dr. J. R. Quinn and other members of the department of ophthalmic surgery, and patients with rheumatic or collagen diseases, studied with Dr. W. D. Robinson and Dr. I. F. Duff in the Rackham Arthritis Research Unit. Responses of surgical patients to standard doses of various corticotropins were examined by Dr. William Coon and Dr. Paul Hodgson of the department of surgery as part of a more general survey of the relationship between adrenal cortex function and the clinical response to major surgery.

All hematologic studies employed heparinized or oxalated venous blood. Eosinophile counts were estimated by a macromodification of Randolph's method, in which 0.2 ml. of blood is pipetted into a small tube containing 3.8 ml. of the phloxine-propylene glycol-water stain and mixed by inversion.

Sedimentation rates were determined by the Westergren method. The chemical serum protein fractionation method of Wolfson and Cohn[15b] was used to estimate true albumin : globulin ratio and individual serum protein components. Following a preliminary autoclaving of urine, as suggested by Wells and Lewis,[19] urine histidine was estimated by Chattaway's adaptation of the Knoop bromination reaction.[15c] Urine urate was determined by the method of Wolfson, Cohn, and Kadota.[20] Urine creatinine was determined by the Bonsnes and Taussky method.[21]

19. Wells, G. S., and Lewis, H. B.: The Histidine Content of the Urine in Pregnancy, Am. J. Obst. & Gynec. **61**:1123, 1951.

20. Wolfson, W. Q.; Cohn, C., and Shore, C.: The Renal Mechanism for Urate Excretion in the Dalmatian Coach-Hound, J. Exper. Med. **92**:121, 1950.

21. Bonsnes, R. W., and Taussky, H. H.: On the Colorimetric Determination of Creatinine by the Jaffe Reaction, J. Biol. Chem. **158**:581, 1945.

Crude neutral urine extracts were used for the estimation of 17-ketosteroid by the method of Robbie and Gibson [22] and for estimation of the Pettenkofer chromogens by the method of Munson and co-workers.[23] Urine corticoids usually were determined by applying a blue tetrazolium reaction [24] to alkali-washed neutral chloroform extracts of urine hydrolyzed at pH 1.[25] Through the cooperation of Dr. William O. Maddock, of Wayne University College of Medicine, urine corticoids in the case of Dr. G. M. were determined as neutral formaldehydogenic lipid. L. E. tests were performed by an unpublished procedure developed to provide a concentrated leucocyte preparation despite the characteristic leucopenia of lupus erythematosus.

ACTX-Corticotropin.—The ACTX preparations were either Purified Corticotropin-Gel (Wilson) or H. P. Acthargel (Armour), both of which are prepared by methods utilizing oxycellulose fractionation. An Organon crude corticotropin with ACTX-like properties was examined, and a few screening studies were carried out with an Upjohn sheep corticotropin prepared without oxycellulose fractionation. These materials are crude in the sense of having a low number of U. S. P. units per milligram but resemble ACTX in having a relatively high ratio of intramuscular to intravenous effectiveness.[26] Wilson and Armour ACTX usually was supplied as a solution of 40 U. S. P. units per milliliter in 15% or 16% gelatin.

Unless otherwise explicitly stated, throughout the present report the potency of all preparations is stated in U. S. P. units as determined by the intravenous rat bioassay method of Sayers, Sayers, and Woodbury, or by one of its modifications. The ACTX-corticotropins currently available commercially are not labeled in U. S. P. units. Armour H. P. Acthargel and Wilson purified Corticotropin-Gel, the two ACTX-corticotropins now being distributed, are labeled in physiological units. In each case 1 physiological unit is equivalent to ⅓ U. S. P. unit.

Aqueous ACTX for the 8 U. S. P. Unit, Four-Hour, Aqueous ACTX Test.—In order to convert the available 16% gelatin solutions of ACTX to essentially aqueous short-acting materials, 10 ml. of the commercial ACTX solution was mixed with 40 ml. of sterile 0.5% phenol to make a solution with 8 U. S. P. units of ACTX per ml. of 3.2% gelatin. Maximum eosinopenia occurred four hours after injection as with ordinary aqueous preparation.

Long-Acting Preparations for Treatment, for Bioassay, and for the 35 U. S. P. Unit, Six-Hour, Long-Acting ACTX Test.—Previous studies [28] had indicated that such light gelatin preparations as the 16% gelatin used in commercial ACTX preparations had a duration of action considerably less than heavy gelatin preparations. A fair comparison required that ACTX be administered in a menstruum comparable to that ordinarily used by us for crude ACTH-corticotropin. This was accomplished by reprocessing the commercial ACTX preparations into materials which contained 5 to 20 U. S. P. units per milliliter of ACTX in a base

22. Robbie, W. A., and Gibson, R. B.: Rapid Clinical Determination of Urinary 17-Ketosteroids, J. Clin. Endocrinol. **3**:200, 1943.

23. Munson, P. L.; Jones, M. E.; McCall, P. J., and Gallagher, T. F.: Colorimetric Method for Estimation of Dehydroisoandrosterone and Its Application to Urine Extracts, J. Biol. Chem. **176**:73, 1948.

24. Chen, C., and Tewell, H. E., Jr.: Corticosteroid Determination with Blue Tetrazolium BT, Fed. Proc. **10**:377, 1951. Henly, A. A.: The Estimation of Corticosteroids, in Annual Report of the West London Hospital, London, West London Hospital, 1951, p. 30.

25. Wolfson, W. Q.; Robinson, W. D., and Hemmerline, A.: Rapid Differential Estimation of the Urinary Metabolites of Hydrocortisone (17-Hydroxy-Corticoids) and Corticosterone (17-Desoxy-Corticoids) by a Simple Microchemical Method, to be published.

26. Hailman, H. F.: Personal communication to the author.

27. Footnote deleted.

28. (*a*) Wolfson, W. Q., and others: The Development, Evaluation and Clinical Use of Long-Acting ACTH Preparations, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2. Therapeutics. (*b*) Wolfson, W. Q., and others: Physiologic and Clinical Studies with Long-Acting Preparations of Pituitary Adrenocorticotrophic Hormone, Univ. Michigan M. Bull. **16**:152, 1950. (*c*) Wolfson.[14b]

containing 28% to 32% gelatin and 0.5% phenol. Such preparations carried the prefix XANG (Armour), XWNG (Wilson), or XUNG (Upjohn) before the lot number on their labels. All ACTX preparations were refrigerated unless actually in use. For use, the vials were warmed under a hot water tap until freely liquid. The necessary dose was then withdrawn and administered deep subcutaneously or intramuscularly through a No. 20 or No. 21 needle. The depot was not massaged after injection. No local irritation or intolerance was caused by these extemporaneous preparations.

Long-Acting Preparations of Crude ACTH-Corticotropin.—The long-acting ACTH preparations used in comparative studies were recently reviewed by Wolfson and Fajans [14b] and have been discussed in detail elsewhere.[29]

RESULTS

1. *The Comparative Potency of Intramuscularly Administered Long-Acting ACTX-Corticotropin and Long-Acting ACTH-Corticotropin in Human Subjects.*—After preliminary screening studies confirmed the reported greater intramuscular effectiveness of ACTX per U. S. P. unit,[11] it became necessary to derive quantitative expressions for the relative potency of ACTX and ACTH, per U. S. P. unit, when these preparations were administered intramuscularly. It was also necessary to determine if this potency ratio varied with the menstruum in which the preparations were given, if it was consistent from manufacturer to manufacturer, and if it varied from lot to lot.

The Use of Sensitive Subjects and Unique Responses in Screening Studies: The evaluation of an unknown preparation begins with a preliminary estimate of potency. For a few days the material is given to patients who will not suffer appreciable harm from slight temporary overtreatment or undertreatment. With experience, a fair estimate of effectiveness is often possible from the patient's mood, disease activity, weight, and body temperature and from such simple laboratory data as total leucocyte counts, direct eosinophile counts, and sedimentation rates.[30]

Certain "sensitive patients" combine a stable daily corticotropin requirement with unusual sensitivity to underdosage or, less often, to overdosage. When overtreated or undertreated some such patients show a characteristic and reproducible sequence of symptoms, which they may be taught to recognize and to use as a basis for prompt and precise dosage adjustment. A trained sensitive patient may be able to conduct a subjective bioassay of an unknown preparation merely by adjusting dosage to maintain an optimal clinical status. The potency of the unknown material is then estimated from a knowledge of the dosage of standard material required to establish a comparable clinical status. Assays with sensitive subjects probably have been most successfully exploited by Kinsell.[31]

29. Wolfson, W. Q., and others: ACTH and Colchicine in the Clinical Treatment of Acute Gouty Arthritis: Physiological Considerations and Review of Therapeutic Results in 51 Attacks, J. Michigan M. Soc. **49**:1058, 1950. Wolfson, W. Q., and others: An Excellently Tolerated, Heat-Stable, Long-Acting ACTH Preparation Suitable for Prolonged and Ambulatory Treatment, J. Clin. Endocrinol. **11**:800, 1951. Quinn, J. R., and Wolfson, W. Q.: Frequent Good Remissions in Previously Unresponsive Eye Diseases Through Individualized Intensive Treatment with Long-Acting ACTH, Am. J. Med. **13**:610, 1952. Wolfson.[28a,b]

30. The use of patients, rather than normal adults, is advisable. Normal persons usually are relatively insensitive to corticotropin; marked prompt mood changes are particularly unusual. The same insensitivity has been noted in patients with localized eye disease who are otherwise healthy.

31. Kinsell, L. W.: The Clinical Application of Pituitary Adrenocorticotrophic and Adrenal Steroid Hormones, Ann. Int. Med. **35**:615, 1951.

A sensitive subject rapidly detected the low intramuscular potency of the one entirely unsatisfactory lot of ACTX encountered during this study, Wilson 84098. This preparation had been assayed by the intravenous method after vialing and appeared to be satisfactory (as it did also when examined by this technique some months later). Its intramuscular inadequacy was found by Dr. G. M., a male physician with disseminated chorioretinitis who had received continuous corticotropin treatment for approximately six months. On 3 U. S. P. units of XWNG-83459 daily his ocular lesion was well controlled. Chart 2 shows several indications that such doses were not homeopathic. For example, each morning, 24 hours after the injection of the previous day, his blood eosinophile count would be between 150 and 250 per cubic millimeter. Six hours after receiving his daily three units, the eosinophile count was between 0 and 20 per cubic millimeter. Increasing or decreasing the daily XWNG-83459 dosage by 1 U. S. P. unit provoked overdosage or underdosage manifestations, respectively. When transferred to XWNG-84098, 3 U. S. P. units per day, the patient recognized signs of ocular relapse within two or three days and began to adjust his dosage upward. At 5 U. S. P. units per day, he had not yet noted an effect comparable to that of XWNG-83459, 3 units per day. Since it was considered unwise to permit him to experiment further, the XWNG-84098 was replaced by a standard preparation which had previously been assayed in man.

This experience led 84098 to be subjected to quantitative human bioassay, using the 8 U. S. P. unit, four-hour, aqueous ACTX test procedure. The results, summarized in Table 3, indicated that 8 U. S. P. units had significantly less intramuscular activity than either 12.5 or 25 U. S. P. units of ACTH. Its actual intramuscular activity appeared to be approximately 31% of the expected value.[32]

Five ACTX preparations judged clinically "satisfactory" had potencies between 97% and 137% of the expected value. Two ACTX preparations judged "substandard" had potencies between 50% and 70% of the expected value. One ACTX preparation judged "entirely unsatisfactory" had a potency 31% of the expected value (Table 3).

These findings would suggest that a 30% to 50% drop in potency is detectable, providing that the clinician is on guard for possible variations in potency.

An increasing number of relapses in patients receiving maintenance treatment gave ample clinical confirmation of the ineffectiveness of 84098.

Chart 2 also shows the usefulness of a uniquely intense metabolic, hematologic, or clinical response as a sign of exceptional potency. In Dr. G. M. 17-ketosteroid excretion increased from 12.5 mg. per day to 82.0 mg. per day and urine formaldehydogenic corticoid rose from 0.6 mg. per day to 18.0 mg. per day in response to a single 50 U. S. P. unit dose of long-acting ACTX. Equally marked responses have never been seen after a single 50 to 100 U. S. P. unit dose of long-acting ACTH.

Assay by Maintenance of Hormonally Induced Remission: Corticotropins may be evaluated by comparing their ability to maintain an established hormonally induced remission in a corticoid-sensitive disorder. The method is illustrated in Chart 3 by data on Mrs. L. K., a woman with subacute disseminated lupus

32. The present data give an interesting indication of the sensitivity of clinical impressions. Most often, the long-acting ACTX preparations were given with the expectation that each U. S. P. unit would replace three U. S. P. units of ACTH; i. e., the intramuscular potency of ACTX was expected to be 300% of that of ACTH.

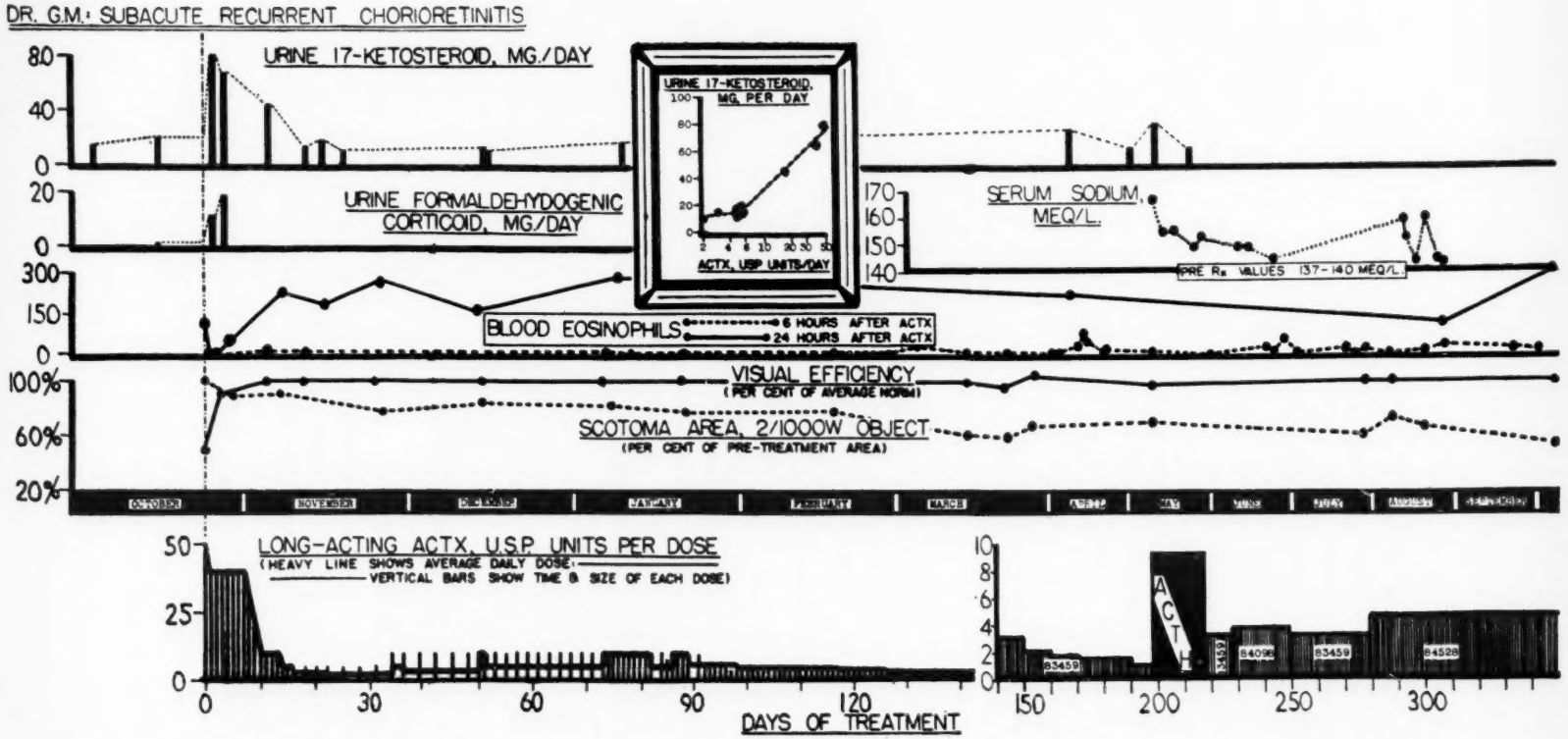


Chart 2.—An example of how sensitive subjects and unique responses may aid in the preliminary evaluation of corticotropins.

This chart summarizes the first year of continuous corticotropin treatment of a patient with subacute recurrent chorioretinitis, right eye. Long-term therapy was made necessary by repeated relapses following termination of brief courses of corticotropin. Normal visual acuity was restored promptly and maintained continuously. A decrease in planimetric scotoma area and restoration of the anatomical continuity of the retina, as viewed ophthalmoscopically, proceeded more slowly and were still continuing at the time this chart was prepared. Supplementary thyroid, potassium chloride, and calcium lactate were given with the corticotropin.

Indications that the patient was a "sensitive subject" included (1) the small daily corticotropin ration which sufficed for maintenance treatment, (2) prompt appearance of overdosage or underdosage symptoms following small increases or decreases in the daily ration, (3) a daily fall in blood eosinophiles of 90% six hours after the daily dose of long-acting hormone was given, (4) maintenance of chronic hypernatremia by small daily doses of corticotropin, and (5) an unusually large increase in 17-ketosteroid output with changes in the log dosage of corticotropin, as shown by the dose: response curve insert.

The "unique response" shown is the striking increase in the 24-hour output of urinary 17-ketosteroid and formaldehydogenic corticoid which followed the initial 50 U. S. P. unit dose of long-acting ACTX-corticotropin.

On the basis of subjective observations, the patient detected the unsatisfactory status of preparation 84098 within a few days after its use was begun.

erythematosus and in Chart 4 by observations on Mr. T. S., a young man with binocular chronic retrobulbar neuritis due to multiple sclerosis. The essential maneuver is transfer of a well-stabilized patient from a known minimum maintenance dosage of a standard ACTH-corticotropin to an unknown ACTX-corticotropin at a dosage preselected as presumably equivalent. The ration of the unknown ACTX-corticotropin is then manipulated to establish the minimum dose required to maintain the degree of remission present before transfer. Ideally, following the period of ACTX administration, the patient is returned to the standard ACTH-corticotropin to demonstrate that maintenance requirements have remained unchanged.

Chart 5 summarizes maintenance of remission data for seven patients (two with disseminated lupus erythematosus, four with chronically active disorders of the posterior ocular segment or optic nerve, and one with rheumatoid arthritis). To all these patients long-acting ACTH or ACTX was given once every 24 to 72 hours. In individual patients, each U. S. P. unit of ACTX-corticotropin appeared therapeutically equivalent to between 1.9 and 4.1 U. S. P. units of ACTH-corticotropin, with a median equivalence of 3.55 U. S. P. units of ACTH-corticotropin.

Quantitative Assay for Therapeutic Potency by Establishing the Relationship Between Intensity of Treatment and Percentage of Remission: Quinn and Wolfson [33] have recently shown that, in a homogenous group of patients, the relationship between the percentage of remissions achieved by corticotropin treatment and the dosage of hormone used resembles many simpler biological dose: response relationships. They were able to distinguish two categories of corticoid-sensitive eye disorders, each of which was characterized by its own dose: response curve and by special clinical characteristics. In the present study this technique has been adapted for assay purposes by determining the form of the dose: response curves obtained when ACTX or ACTH is employed in the definitive treatment of patients with serious disorders of the posterior ocular segment or optic nerve.

Chart 6 summarizes the assay results obtained. The percentage of remissions (i. e., the "response") is plotted on the vertical axis. The maximum daily corticotropin requirement found necessary to establish remission is plotted on a logarithmic scale (i. e., the "log dose") on the horizontal axis. To minimize the effect of high dosages continued only for one or two days, "maximum daily corticotropin requirement" has been defined as the largest average daily corticotropin dosage used in any 10-day treatment period. Both the ACTH and ACTX curves have the sigmoid shape characteristic of biological log dose: response curves and both also show the approximate linearity over a long middle range which is most suitable for assay use. In addition, over a long middle range, the ACTH: response and ACTX: response curves are parallel. According to accepted convention, such identity of slope suggests an absence of qualitative differences and indicates the existence of a constant ratio between the potency of ACTX and that of ACTH. The value for this potency ratio is approximately 3.20 and may be estimated by graphic comparison of the dosages of ACTH and ACTX which will yield an identical frequency of remission. Thus, each U. S. P. unit of long-acting ACTX

33. Quinn, J. R., and Wolfson, W. Q.: Improved Results from Individualized Intensive Hormonal Treatment in Certain Eye Diseases Reported to Respond Poorly to ACTH or Cortisone, Univ. Michigan M. Bull. **18**:1, 1952.

appears to produce therapeutic effects equivalent to those of approximately 3.20 units of long-acting ACTH.

Assay for Comparative Metabolic Effectiveness Using Interspersed Comparison Techniques: Certain metabolic indices showing relatively constant displacement with changes in circulating 11,17-oxysteroid level are followed. Most useful are

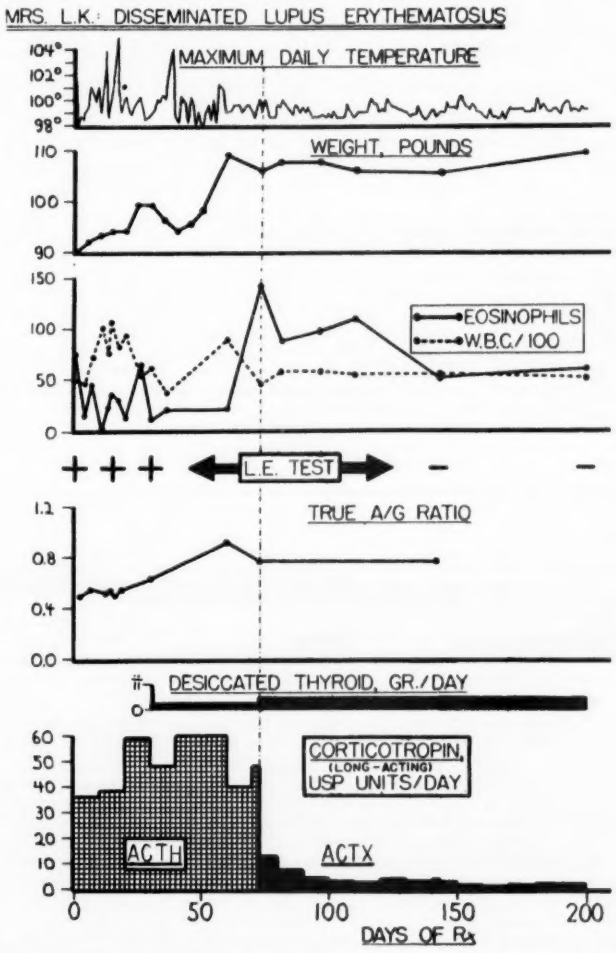


Chart 3.—Maintenance of ACTH-induced remission by small doses of ACTX-corticotropin, which efficiently maintained clinical status, prevented temperature elevations, permitted maintenance of normal body weight, and corrected abnormal serum protein patterns to some extent, as indicated by a rise in true albumin: globulin ratio and return of the abnormal L. E. test to normal.

the urinary excretion of urate, histidine, and certain steroid metabolites (17-ketosteroids, Pettenkofer chromogens, and neutral blue-tetrazolium-reducing corticoids). Values generally are expressed relative to urine creatinine. These metabolic indices are first examined during administration of a particular dosage of standard cortico-

tropin, next during administration of the unknown corticotropin at a level of dosage anticipated to produce metabolic effects identical with those of the first period, and finally during repetition of the dosage and preparation of the first period. The more closely the preliminary estimate of the potency of the unknown preparation approximates its actual potency, the more accurate such assays become. For this reason, metabolic assays are generally deferred until some familiarity with a particular preparation has been acquired. Other basic considerations and the technique of calculation employed are discussed more fully elsewhere.[28a]

The metabolic assay summarized in Chart 7 compared the intramuscular potency of Armour K29601 (an ACTH-corticotropin prepared by isoelectric precipitation), Lilly 190-4B-142 (an ACTH corticotropin made by the Astwood glacial-acetic-acid process), and Wilson 82179 (an early experimental ACTX preparation). The two

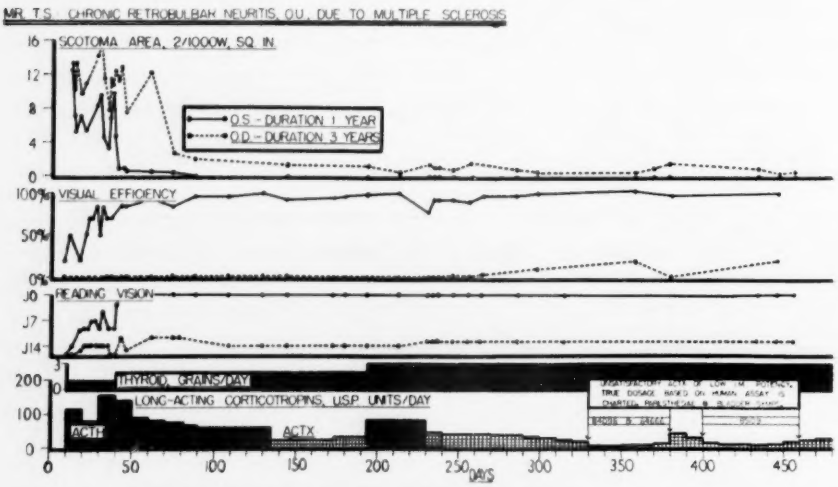


Chart 4.—Establishment and maintenance of remission by long-acting ACTH-corticotropin and ACTX-corticotropin in chronic retrobulbar neuritis due to multiple sclerosis.

The chart shows the first 500 days of continuous corticotropin treatment in a young man with chronic retrobulbar neuritis, in each eye, due to multiple sclerosis. Treatment rapidly resulted in restoration of normal vision in the left eye, which presented defects of approximately one year's duration. Improvement in the right eye has proceeded more slowly, and a small residual central scotoma still largely prevents high-acuity central vision. No observable progression of extraocular multiple sclerosis symptoms has occurred during this study. Temporary exacerbations due to local heating, recently reported to be characteristic of multiple sclerosis, were prominent manifestations of this patient's ocular disorder but gradually disappeared during treatment.

The remission established at a daily corticotropin dosage of 160 units per day of ACTH continued without interruption when dosage was reduced to 80 units per day of long-acting ACTH and when this was replaced by 25 or 30 units per day of long-acting ACTX. At this point, on approximately the 190th treatment day, an attempt was made to return the patient of 90 units per day of long-acting ACTH. A prompt increase in scotoma area and decrease in visual acuity, in each eye, indicated that this dose of long-acting ACTH no longer was adequate. Remission was reestablished by returning the patient to long-acting ACTX at a temporarily increased dosage level.

This patient also was treated with each of the three substandard lots of ACTX-corticotropin at periods between the 330th and 460th treatment days. The dosages shown on the chart represent the amount of hormone actually given after correction for substandard extravascular efficiency. These unintentionally low dosages did not markedly interfere with visual function but did permit the temporary appearance of paresthesiae and bladder symptoms.

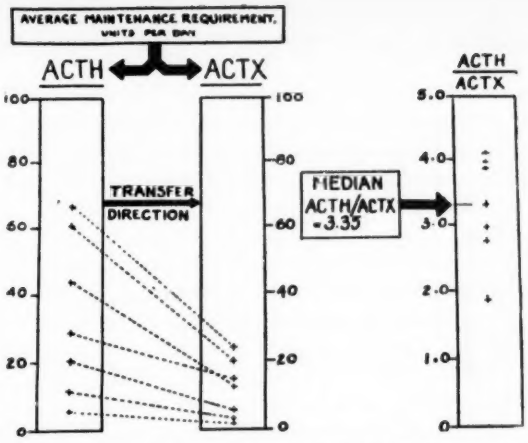


Chart 5.—Comparative ability of long-acting ACTH and ACTX to maintain an established hormonally induced remission. Seven patients with well-stabilized hormonally induced remissions were transferred from long-acting ACTH to long-acting ACTX. Both preparations were given in similar menstrua and at similar time intervals. The dose of long-acting ACTX was manipulated to provide a level of therapeutic control approximately equivalent to that obtaining before transfer, and, usually, the equivalence was checked by a second period on the long-acting ACTH preparation. The data obtained from studies of this type are comparatively crude at best, however. In these seven patients, each U. S. P. unit of long-acting ACTX appears approximately equivalent to from 1.9 to 4.1 U. S. P. units of long-acting ACTH, with a median equivalence of 3.35 units of ACTH per unit of ACTX.

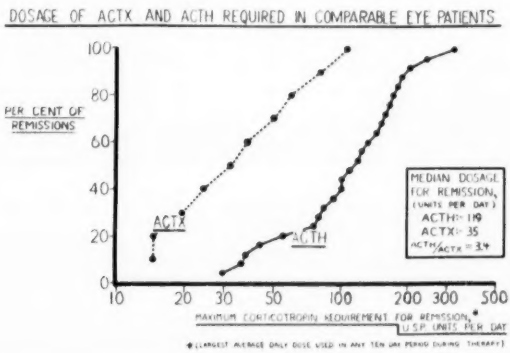

DOSAGE OF ACTX AND ACTH REQUIRED IN COMPARABLE EYE PATIENTS
PER CENT OF REMISSIONS
ACTX
ACTH
MEDIAN DOSAGE FOR REMISSION, (UNITS PER DAY)
ACTH= 119
ACTX= 35
ACTH/ACTX = 3.4
MAXIMUM CORTICOTROPIN REQUIREMENT FOR REMISSION,* U.S.P. UNITS PER DAY
*(LARGEST AVERAGE DAILY DOSE USED IN ANY TEN DAY PERIOD DURING THERAPY)

Chart 6.—Direct comparative bioassay of corticotropins for therapeutic potency.

The basic datum determined in this study was the maximum daily corticotropin dosage required to induce sustained remission when a previously untreated patient with a serious disorder of the posterior ocular segment or optic nerve received definitive treatment with either long-acting ACTH or long-acting ACTX. In order to avoid discrepancies resulting from high dosages given for only one or two days, "maximum daily corticotropin dosage" has been defined as the largest average daily dose of corticotropin required for any 10-day period during treatment.

The chart is read as follows: Ten patients received definitive treatment with ACTX. The first and second patients required a maximum daily corticotropin dosage of 14.5 units per day, the third required 19.5 units per day, the fourth 24 units per day, and so forth, until all 10 have been accounted for. It is apparent that there exists a relationship between the percentage of remissions and the logarithm of maximum corticotropin dose requirements which is approximately linear over a long middle range.

There exists a good parallelism between the ACTX and ACTH curves over the middle range, implying the existence of a quantitative difference in their potencies without important qualitative differences. An exact figure for this difference may be obtained by plotting the dosages of ACTX and ACTH which give equal frequencies of remission. Such a plot shows each U. S. P. unit of ACTX to be an approximate equivalent of 3.20 U. S. P. units of ACTH in its ability to induce remission in this standard group of patients.

Reference to Chart 8 will show a similar parallelism between the curve describing the relationship of logarithm of long-acting ACTH dosage to 24-hour eosinopenic responses and the curve relating the logarithm of long-acting ACTX to 24-hour eosinopenic responses.

crude ACTH preparations were aqueous solutions, while the ACTX was a 16% gelatin solution. All materials were given intramuscularly, one-fourth of the daily dose every six hours. In the third study period, the patient received 50 U. S. P. units of ACTH per day. In the fourth period, he was given 10 U. S. P. units of ACTX per day. Marked symptomatic improvement and rather striking euphoria were immediate indications of the superior potency of the ACTX preparation. Laboratory confirmation was obtained first from the additional fall in circulating eosinophile level and later from the large increases in 17-ketosteroid, Pettenkofer chromogen, and histidine excretion during the fourth period. Calculated potencies suggested that each U. S. P. unit of the Wilson ACTX was the metabolic equivalent of approximately 8.18 units of the Armour ACTH or 6.50 units of the Lilly ACTH. The Lilly ACTH appeared to be approximately 1.25 times as effective per unit as the Armour ACTH, a finding consistent with previous studies, in which glacial-acetic-acid process crude ACTH was compared with crude ACTH obtained by isoelectric precipitation.

While the study of Figure 7 seems to yield apparent potencies for ACTX much higher than those of other studies, this result actually is an artifact resulting from an error in technique. The ACTH preparations were given as aqueous solutions, while the ACTX was dissolved in 16% gelatin. In a previous unpublished study Wolfson, Robinson, and Duff [6] confirmed the observation of M. Landa Bacallao [34] that, when both preparations were given intramuscularly on an identical time schedule of dosage, corticotropin in 16% gelatin was almost precisely twice as effective as the same corticotropin given as an aqueous solution. To correct for differences in menstrua, the potency ratios calculated from the data of Figure 7 must be halved. The observations actually suggest intramuscular administration of one U. S. P. unit of the ACTX preparation to be approximately 3.25 times as effective as each unit of the Lilly ACTH and 4.14 times as effective as each unit of the Armour ACTH.

Seven metabolic bioassays have been carried out by this interspersed comparison method on five different lots of ACTX-corticotropin. The potencies calculated for individual lots varied from 256% to 414% of standard. The average data for the five lots studied suggested that one U. S. P. unit of intramuscularly administered ACTX-corticotropin produces metabolic changes equivalent to those of 3.46 U. S. P. units of intramuscularly administered ACTH-corticotropin.

Rapid Assay of Long-Acting Corticotropins for Hematologic Efficacy by the 24-Hour Eosinopenia Method (Method of Sustained Eosinopenia): A rapid evaluation of long-acting corticotropins may be obtained by comparing their ability to produce eosinopenia which persists 24 hours after a single standard dose. A recent study by Wolfson and Fajans [14b] used this procedure to evaluate the effect of different retarding menstrua upon the duration of action of corticotropins. Their results paralleled those previously obtained by metabolic bioassay.[25a]

In practice, the method is extremely simple. Data must be obtained on a group of 10 to 20 subjects, but either normal adults or patients may be used. However, subjects must not receive exogenous corticotropin or cortisone within one week of study. On the first morning of the test, blood is drawn for an eosinophile count and the test dose of long-acting corticotropin given immediately thereafter. The depot

34. Landa Bacallao, M.: Personal communication to the author.

preparation should be given deep subcutaneously rather than intramuscularly, if possible, and the depot should not be massaged after injection. The following morning, as nearly as possible 24 hours after administration of the test dose, the second eosinophile count is obtained. From the two eosinophile counts, the 24-hour drop in eosinophile level is calculated (i. e., if the initial count is 250 per cubic millimeter and the 24-hour count is 50 per cubic millimeter, the drop is minus 80%).

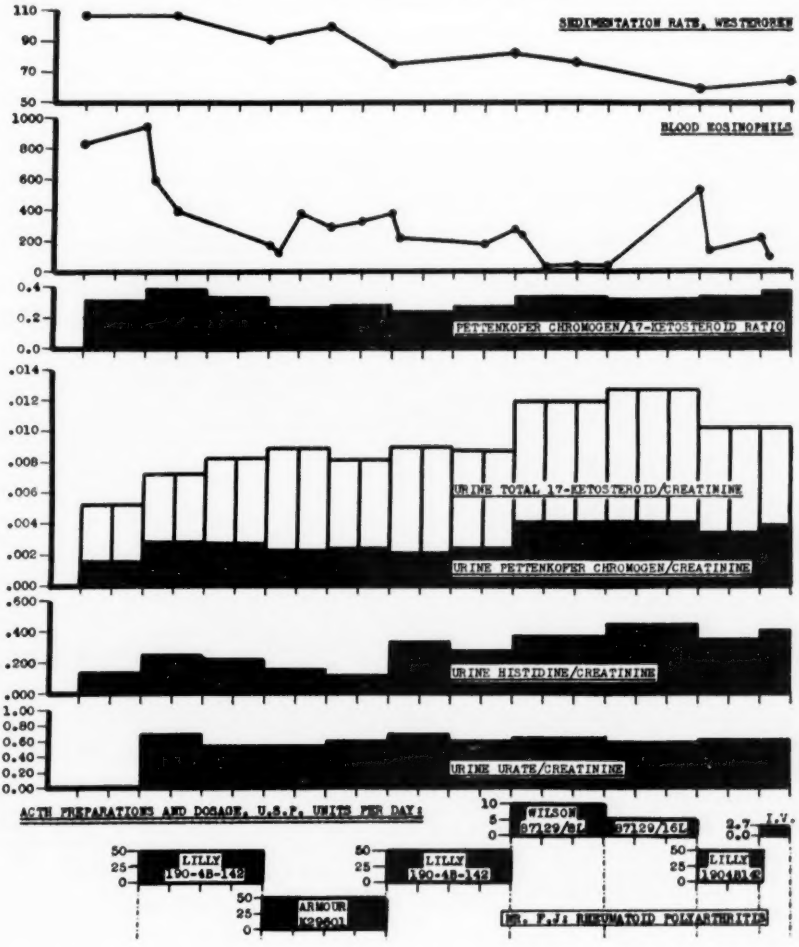


Chart 7.—Comparative evaluation of corticotropins by means of semiquantitative metabolic bioassay. All corticotropins studied were given intramuscularly, one-quarter of the daily ration every six hours. Armour K29601, taken as the standard, is an isoelectric precipitated crude ACTH and was given as an aqueous solution. Lilly 190-4B-142, a glacial acetic acid processed crude ACTH, also was given as an aqueous solution. Wilson 82179, an ACTX-corticotropin eluted from oxycellulose columns, was given in 16% gelatin. Evaluation of the results of this study is considered in detail in the text.

Table 1 summarizes data obtained with long-acting ACTH- corticotropins and long-acting ACTX-corticotropins. The parallelism between median 24-hour eosino-

penia and the percentage of subjects who manifest a 24-hour eosinophile count less than 50% of the initial count should be particularly noted, since, for statistical estimation of significance, average or median eosinopenic response is a less useful datum than is the percentage of subjects showing a 50% or greater fall in eosinophiles.

Table 1 shows that a 33 to 35 unit dose of ACTX in 28% gelatin produces a higher percentage of "50% responders"[35] and a more profound median 24-hour eosinopenia than 100 units of any long-acting crude ACTH except Adactar, prepared from glacial-acetic-acid-processed crude ACTH. It has been noted earlier that the intramuscular potency of the latter is about 1.25 times that of the standard isoelectric-precipitated ACTH per U. S. P. unit. When the log dose: response curves

TABLE 1.—*Twenty-Four Hour Eosinopenia After Single Doses of Long-Acting Corticotropins: Effect of Altering Hormone Subtype, Infection Menstruum, or Dosage*

Subjects, No.	Type of Corticotropin Studied,* Dose, Units	24 Hr. Decrease in Blood Eosinophiles of Median Subject % of Initial Level	Subjects with 50% or Larger 24-Hr. Drop in Eosinophiles Subjects, %	Estimated Equivalent Dose of Isoelectric-Precipitated Adactar U.S.P. Units
Long-acting ACTH-corticotropins				
19	100 U. Adactar (glacial acetic ACTH)	—93	84	119
53	100 U. Adactar (isoelectric ppt.† ACTH)	—85	70	100
20	100 U. Adactar tannate	—81	70	98
14	100 U. ACTH in heavy gelatin ‡	—69	64	86
22	100 U. Adactar-0-40 (Acthar in oil)	—55	55	71
6	100 U. ACTH in light gelatin ‡	—27	33	54
31	40 U. Adactar (isoelectric ppt.† ACTH)	—13	6	40
ACTX-corticotropin in 28% gelatin §				
6	40 U. ACTX in 28% gelatin	—100	100	..
24	33-35 U. ACTX in 28% gelatin	—85.5	83	108
11	20-25 U. ACTX in 28% gelatin	—39	45.5	63

* Adactar is corticotropin adsorbed on colloidal aluminum phosphate and suspended in polyvinylpyrrolidone. Adactar tannate is identical, except that corticotropin tannate is used as starting material. Adactar-0-40 (Acthar in oil) is corticotropin suspended in aluminum monostearate and oil. Additional information on these preparations may be found in a recent report by Wolfson and Fajans.[14b]

† Ppt. = precipitated.

‡ "Light" gelatin preparations become liquid when held in the fist for a minute or two and may then be given through a No. 23 needle; the gelatin concentration has generally been 15 to 23%. "Heavy" gelatin preparations must be heated for a period beneath the hot water tap before they can be given through a No. 21 needle; their gelatin concentration has been 24 to 32%.

§ A 33 to 35 unit dose of ACTX in 28% gelatin produces a 24-hour eosinopenia of about the same intensity and somewhat more regularity than is induced by a 100 unit dose of Adactar processed from isoelectric precipitated ACTH-corticotropin (the reference standard). If the dose: response curves of Chart 8 are used to obtain a more precise estimate, it may be calculated that 1 U.S.P. unit of ACTX in 28% gelatin produces a sustained eosinopenia comparable to that of approximately 3.19 U.S.P. units of Adactar prepared from isoelectric precipitated crude ACTH-corticotropin, provided that both preparations are given intramuscularly. This estimate of potency may be considered conservative, since heavy gelatin is actually a somewhat less effective retarding menstruum than the Adactar menstruum.

(Chart 8) are utilized to obtain a more exact estimate, each U.S.P. unit of ACTX in 28% gelatin appears to produce 24-hour eosinopenia equivalent to that induced by 3.19 U.S.P. units of Adactar.

The data of Table 1 also suggest a rapid method for screening corticotropins for ACTX properties. Only 2 of 31 subjects given 40 U.S.P. units of Adactar pre-

35. "50% Responders" show a 50% or greater eosinophile drop under a particular set of conditions. In the present context, it refers to those subjects who show a 50% or greater eosinophile drop 24 hours after receiving a particular dose of corticotropin.

pared from crude ACTH had a 24-hour eosinophile count below 50% of the pretreatment count. However, 25 of 28 subjects given 33 to 35 or 40 unit doses of ACTX in 28% gelatin had 24-hour eosinophile counts less than 50% of the pretreatment level. Statistical analysis utilizing the χ-square test shows less than a 1 in 100 possibility ($P < .01$) that the observed differences in response are due to chance. The 24-hour eosinopenic response to 40 U.S.P. units of an unknown corticotropin in menstrua comparable to Adactar or 28% gelatin will rapidly indicate whether or not the material studied falls into the ACTX or ACTH category.

Summary of Assay Data on Long-Acting ACTX-Corticotropin: Table 2 summarizes the observations on long-acting corticotropins. There appears to be close parallelism between the ability of the two corticotropin subtypes to evoke various physiological alterations. In each of these activities, one U. S. P. unit of ACTX-corticotropin is approximately three times as effective as one U. S. P. unit of ACTH-corticotropin when both are given intramuscularly. The average ratio of intramuscular ACTX potency to that of ACTH varies from 3.19 to 3.46, depend-

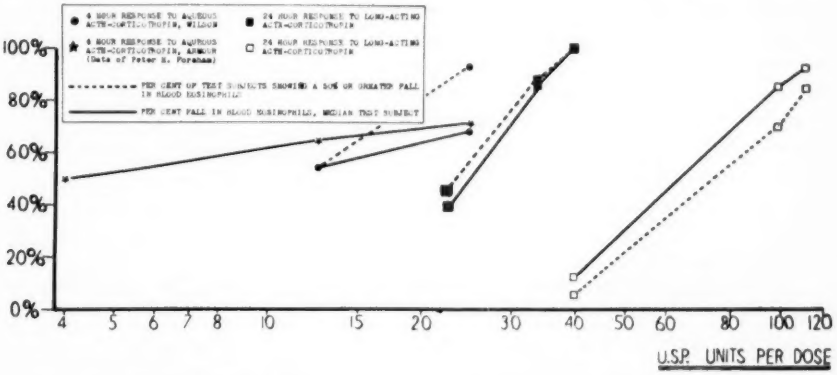


Chart 8.—Relationship of logarithm of corticotropin dosage to four-hour eosinopenic responses following aqueous ACTH and to 24-hour eosinopenic responses after long-acting ACTH (Adactar) and long-acting ACTX (ACTX in 28% gelatin).

ing upon the technique of evaluation, with an over-all average of 3.30. This relatively good agreement suggests that there are few qualitative differences between ACTX and ACTH preparations.

2. *Tests of Adrenal Cortex Function Employing Intramuscular Aqueous and Long-Acting ACTX-Corticotropins: Use of Aqueous Preparations in the Comparative Evaluation of ACTX and ACTH Potencies.*—In 1948, Thorn and his associates [36] described the metabolic and hemotologic changes which followed the intramuscular administration of a single 25 unit dose of aqueous crude ACTH. A fall in blood eosinophile count four hours after administration and a concomitant rise in the urine urate: creatinine ratio regularly were found in normal subjects but not in patients with primary or secondary deficiencies of adrenal function.

36. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15, 1948. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal-Cortical Insufficiency: The Response to Pituitary Adrenocorticotrophic Hormone, J. A. M. A. **137**:1005, 1948.

They therefore suggested the use of these four-hour responses to a 25 unit dose of ACTH as a test of adrenal cortical "reserve" (more properly, perhaps, "responsiveness"). This procedure has come to be known quite generally as the "Thorn test."[37]

Two factors have made it desirable to develop a test with intramuscular ACTX which can be used as a direct substitute for the original Thorn test. An increasing number of persons give false negative responses to the Thorn test because previous administration of crude ACTH has led to a heightened ability to inactivate ACTH given intramuscularly.[21] In addition, an occasional false negative appears to be due to excessive extravascular inactivation without previous exposure to ACTH. Renold and his associates estimate that 8% of patients who have previously received two or more courses of crude ACTH treatment will show significantly increased extravascular inactivation of ACTH, but Meyer, on the basis of data made available to the Armour Laboratories, feels that partial resistance may occur in

TABLE 2.—*Long-Acting ACTX vs. Long-Acting ACTH in Man*

		% of Acthargel K47721 or Adactar
ACTX in 26%-32% gelatin I.M. every 24 hr.		
Metabolic bioassay, average		346
XANG-377207	321%	
XWNG-83459	280%	
XANG-377241	332%, 422%, 337%	
XWNG-82179	414%	
Sustained eosinopenia		319
Induction of remission in standard patients		320
Maintenance of hormonally induced remission		335
Average		330
ACTX in 15%-23% gelatin I.M. every 24 hr.		
Metabolic bioassay (83285)		256
Sustained eosinopenia		218
Average		237

* ACTX in heavy gelatin = 1.4 (ACTX in light gelatin).

up to 20% of such patients. As yet, however, ACTX has not been observed to produce a similar refractoriness to its subsequent intramuscular administration. A second more practical consideration is the likelihood that, in the relatively near future, ACTX preparations will displace ACTH from the commercial market.

The 8 U. S. P. Unit, Four-Hour, Aqueous ACTX Test: The 8 U. S. P. unit, four-hour, aqueous ACTX test has been designed to provide stimulation of the adrenal cortex equal to the 25 U. S. P. units of ACTH used in the original Thorn test. In the present studies, only the four-hour change in circulating blood eosinophiles was measured. To obtain successive groups of approximately similar composition, all tests were carried out on unselected consecutively admitted patients of the department of surgery. Each patient's test was begun as soon as practicable after admission. No patient had more than one test (but patients who failed to show a

37. The term "Thorn test" is often incorrectly applied to the four-hour test of the eosinopenic response to 0.3 mg. of l-epinephrine. Actually, on a number of occasions Dr. Thorn publicly criticized the rather scanty evidence on which this procedure was accepted as a test of hypothalamo-pituitary-adrenal function, a position which has subsequently proved to be quite justified.

50% eosinopenia were retested with the 35 U. S. P. unit, six-hour, long-acting ACTX test).

Evaluation of the 8 unit ACTX test required its comparison with the response to standard doses of ACTH in a similar group of patients. For this purpose 28 patients were given 12.5 U. S. P. units of Wilson crude corticotropin and 73 patients were given 25 U. S. P. units of the same preparation.

Chart 8 summarizes dose: response data for four-hour eosinopenic responses to aqueous ACTH and for 24-hour eosinopenic responses to Adactar (crude ACTH) and to long-acting ACTX. In this graph, log dose is compared with two types of response: (1) the degree of eosinopenia exhibited by the median subject given a particular dose and (2) the percentage of subjects given a particular dose who showed a 50% or greater drop in eosinophiles when the post-treatment blood sample was taken. The two types of response show close parallelism in the case of long-acting ACTH and long-acting ACTX. However, in the case of the four-hour response to aqueous ACTH, the median eosinopenic response to 12.5 units is only slightly inferior to the response to 25 units, while there is a considerable difference between the percentage of subjects showing a 50% or greater eosinopenia at the two dose levels. For this reason, the "percentage of 50% responders" is the more sensitive index in the 12.5 to 25.0 unit dose range employed with aqueous corticotropins.

Table 3 summarizes the four-hour eosinopenic responses to standard doses of crude ACTH, to three clinically unsatisfactory lots of ACTX, to five clinically satisfactory lots of ACTX, and to one interesting Organon preparation, which although chemically crude resembled an ACTX-corticotropin in behavior. The probability that the results obtained with each lot of ACTX are significantly different from those given by 12.5 or 25 units of ACTH have also been calculated. Two hundred and fifteen patients received 8-unit test doses from one of the six clinically satisfactory lots of ACTX. Seventy-nine per cent (169 of 215) of the patients showed a 50% or greater eosinophile decrease after the test dose, while a somewhat larger percentage of 50% responses was obtained with the 25 unit test dose of Wilson crude corticotropin (which, it should be recalled, actually represents 31.25 units of standard crude ACTH). The patients given 8 units of satisfactory ACTX showed a median 66% decrease in eosinophiles four hours after the test dose, while those receiving 25 units of Wilson crude ACTH showed a median 68% decrease. Statistical analysis by the χ-square method shows no significant difference between the response to 8 units of satisfactory ACTX and that to 25 units of crude ACTH. However, there is less than 1 in 100 chance ($P < .01$) that the response to 8 units of ACTX is not significantly different from the response to 12.5 units of crude ACTH.

The dose: response curve of Chart 8 may be used to obtain a more precise estimate of the potency of the 8 unit dose of ACTX from clinically satisfactory lots. The estimated equivalent of 8 units based upon the percentage of 50% responders is 19.7 units of Wilson crude ACTH which, in turn, is equivalent to 24.6 U. S. P. units of standard isoelectric-precipitated crude ACTH. The estimated potency based upon median eosinopenia is 21.5 units of Wilson crude ACTH, which is equivalent to 26.8 U. S. P. units of standard crude ACTH. Thus, on the average, the four-hour eosinopenic response to 8 U. S. P. units of ACTX given intramuscularly suggests this dose to be the physiological equivalent of 25.7 U. S. P.

units of intramuscularly administered standard isoelectric-precipitated crude ACTH. Each U. S. P. unit of intramuscularly administered ACTX appeared to

TABLE 3.—*The 8 U. S. P. Unit, Four-Hour, Intramuscular, Aqueous ACTX Test: Quantitative Evaluation of Aqueous Corticotropins by Four-Hour Eosinopenia*

Subjects, No.*	Preparation and Dosage: U. S. P. Units	Preparation and Dosage: Lot No.	Eosinopenia in Median Subject; Fall in 4 Hr., %	Subjects with 50% or Larger Drop in Eosinophiles; Subjects, %	Probability (P Value) † that Results Differ Significantly from: 12.5 U. Crude ACTH	Probability (P Value) † that Results Differ Significantly from: 25.0 U. Crude ACTH	Estimated Average I. M. Potency U. S. P. Unit ‡; Crude ACTH-A, Armour, %
Crude ACTH-corticotropin, Wilson ("corticotropin, crude," "U. S. P. corticotropin") §							
28	12.5	.....	—54.5	54	....	0.02	125 ‖
73	25.0	.....	—68	93	0.02	....	125 ‖
Clinically satisfactory ACTX-corticotropins ("corticotropin, purified," "high-potency corticotropin")							
55	8	84719	—62	77	0.05	NS ¶	290
43	8	377241	—64	84	0.01	NS ¶	325
45	8	84528	—67	80	0.02	NS ¶	339
30	8	85603	—70	77	0.07	NS ¶	363 ‡
13	8	491115	—70	85	0.05	NS ¶	384 ‡
215	8	All satisfactory ACTX lots **	—66	79	0.01	NS ¶	329
A crude corticotropin, Organon, which exhibits characteristic ACTX-corticotropin activity							
29	8	233714	—67	76	0.08	NS ¶	329 ‡
Clinically unsatisfactory ACTX-corticotropins							
25	8	84098	—32	28	0.05	0.01	93 ††
30	8	85109	—46.5	47	NS ¶	0.01	151 ††
50	8	84666	—54.5	62	NS ¶	0.01	210
105	8	All unsatisfactory ACTX lots	—47	49.5	NS ¶	0.01	165 ††

* All observations were made on unselected consecutively admitted surgical patients, who were tested as soon as possible after admission. Patients who previously had received any form of corticotropin were excluded. Patients who failed to show a 50% four-hour eosinopenia after 25 units of crude ACTH or 8 units of ACTX generally were retested later with the 35 U.S.P. units, six-hour, long-acting ACTX test. Studies on surgical patients were supervised by Dr. William Coon and Dr. Paul Hodgson of the Department of Surgery and these data are reproduced through their cooperation.

† P values were estimated by applying the χ-square test to the data on percentage of subjects who showed a 50% or better four-hour decrease in eosinophiles. It is apparent from these data that 8 U.S.P. units of a satisfactory ACTX-corticotropin produces a four-hour eosinopenia which is statistically indistinguishable from the eosinopenic response to 25 U.S.P. units of crude ACTH, the dose used in the Thorn test.

‡ Average intramuscular potency was estimated as follows:

1. Empirical log dose: response equations were derived from the two-level responses to crude ACTH-corticotropin, as follows:
   Log dose = 0.0223 (4-hr. eosinopenia in median subject) —0.022.
   Log dose = 0.00773 (percentage of 50% responders) +0.776.
2. The data observed for any unknown hormone preparation were then substituted in these equations to find the apparent dose of crude ACTH necessary to reproduce the effects of the dose actually given, which ordinarily was 8 U.S.P. units. From this, it was possible to calculate the amount of crude ACTH equal to 1 U.S.P. unit of the unknown material.

§ The Wilson crude ACTH-corticotropin used to establish the standard responses to 12.5 and 25 units of crude ACTH was pooled from several production lots, each of which, in turn, was itself pooled from several primary lots. This material may therefore be considered a good sample of average production.

‖ The standard corticotropin to which our studies are referred is an Armour crude ACTH-corticotropin prepared by isoelectric precipitation. Wilson crude ACTH is prepared by the Astwood glacial acetic acid process. In our experience (e. g. Chart 7) the acetic acid processed crude corticotropins have consistently been found 115% to 135% as effective per U.S.P. unit as the isoelectric-precipitated crude materials when both were given intramuscularly. Similar impressions have been obtained in a number of other laboratories. For this reason, we have calculated the intramuscular potency of Wilson crude ACTH as 125% of standard rather than 100%.

¶ NS = P value not significant.

‡ One of the two estimates of potency required extrapolation of the log dose : response curve.

†† Both of the estimates of potency required extrapolation of the log dose : response curve.

** Includes observations on Organon 233714, a crude corticotropin with ACTX-corticotropin characteristics.

be equivalent to 3.21 U. S. P. units of intramuscularly administered ACTH. Since this value is almost identical to the average value obtained by comparing the two

corticotropin subtypes in long-acting menstrua, it may be concluded that so long as both materials are given in the same menstruum they may equally validly be assayed as aqueous or as long-acting materials. In addition, the results show that interaction with the long-acting medium plays no part in the superior intramuscular potency of ACTX-corticotropins. Finally, since the eosinopenic response to 8 units of satisfactory ACTX is statistically indistinguishable from the response to 25 units of crude ACTH, it may be concluded that the 8 U. S. P. unit, four-hour, aqueous ACTX test appears to be an entirely satisfactory replacement for the 25 unit Thorn test with crude ACTH.

A more detailed study of Table 3 shows that the satisfactory lots of ACTX had potencies which fell within a relatively narrow range and that each was significantly different statistically from the 12.5 U. S. P. unit dose of crude ACTH. The data on the clinically unsatisfactory lots is particularly interesting. Each of these lots was submitted to exact human bioassay because of poor clinical results. The data show clearly why the clinical results were poor. Eight units of one lot, considered grossly unsatisfactory, were significantly less potent than the 12.5 unit dose of crude ACTH, while the other two lots, considered clinically substandard, were indistinguishable from the 12.5 unit dose of crude ACTH. In addition to the human bioassays each unsatisfactory lot was also submitted to animal subcutaneous assay. The results, presented in a later section, completely confirmed the clinical impression and human bioassay. However, the most significant fact about each of these clinically unsatisfactory lots is that, despite their marked loss of extravascular potency, they continued to show approximately the expected potency on intravenous bioassay by the currently accepted method. Such findings reemphasize the fact that the intravenous bioassay potency of corticotropins is no guarantee of any particular level of intramuscular potency.

The 35 U. S. P. Unit, Six-Hour, Long-Acting ACTX Test: The original purpose of the Thorn test was the detection of those persons whose adrenals were incapable of a prompt response to stimulation. This group is not limited to patients with primary hypoadrenocorticism due to destruction or cytotoxic contraction (Addison's disease) or to a primary defect in steroidogenesis (e. g., salt-losing congenital virilism). Failure to respond to the initial corticotropic stimulation is commonly equally profound when the adrenal cortex has undergone involution because of the absence of corticotropic stimulation (panhypopituitarism, "basophile failure,"[38] "hypopituitarism-with-respect-to-ACTH,"[39] long-term cortisone treatment). A marked diminution in adrenal responsiveness ("myxedema of the adrenal cortex") may result from spontaneous, postoperative, or corticogenic hypo-

38. Maddock, W. O.; Leach, R. B., and Myers, G. B.: "Basophil Failure," A Syndrome Characterized by Failure of ACTH and Gonadotropin Secretion Associated with Intact Thyrotropin Secretion, J. Lab. & Clin. Med. **38**:924, 1951.

39. Case Report: Some Effects of Chronic ACTH Administration in a Patient with Tophaceous Gout, Fall Hay Fever, Hypersensitivity to Colchicine, (and Hypopituitarism-with-Respect-to-ACTH), in Wolfson, W. Q., and Cohn, C.: The Role of the Pituitary Adrenocorticotrophic Hormone (ACTH) and of Adrenal Cortical Steroid Hormones in the Pathological Physiology and Experimental Therapeutics of Clinical Gout, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 263.

thyroidism.[40a] However, experience has shown that only a few of the patients who fail to give a normal response to a single Thorn test actually have any of these disorders.

Data from this laboratory illustrate the high frequency of false negative responses to the Thorn test. In one series of studies, failure to show a 50% drop in blood eosinophiles after 25 mg. of crude ACTH was observed in 18% of normal adults, 55% of patients with gout, and 67% of patients with rheumatoid arthritis.[40b] These studies were carried out during 1950 and 1951 when the available ACTH was irregular in quality, and this may account for a portion of the findings. However, of the 293 patients given the best available crude ACTH (25 units) or ACTX (8 units) during the present study, 18% (52 patients) showed a subnormal response. A high percentage of abnormal responses is, of course, not intrinsically objectionable if correlated with a clinically significant deficiency in function. However, while there is some reason to believe that gout patients may respond inadequately to some types of acute stress,[39] this is not true of most patients with rheumatoid arthritis. A preliminary survey of the clinical protocols by Drs. Coon and Hodgson suggests that major surgery was better tolerated by the patients who did not respond satisfactorily to the Thorn test than by other patients. This result was not entirely unexpected. Fifteen randomly selected patients from the 52 with inadequate Thorn test responses were retested before operation with a 35 unit dose of gelatin-ACTX, as described below, and all but one showed a normal response. Thus, the great majority of abnormal Thorn test responses must be considered "clinical false negatives," i. e., without clinical significance. However, while negative responses to the Thorn test merely indicate the need for further study, positive responses establish a presumption of adequate adrenal cortex sensitivity.

Two newer procedures attempt to remedy the defects of the original Thorn test. Both are based upon the assumption that more intense, repeated stimulation will activate adrenals which fail to respond to 25 units of aqueous ACTH but that even maximal stimulation will not activate absent or seriously involuted adrenals. The 48-hour ACTH test employed eight doses of aqueous ACTH given intramuscularly at six-hour intervals. The initial dose was 25 units, and subsequent doses were 10 units each. Growing awareness of false negative responses due to intramuscular refractoriness led this test to be replaced by the intravenous ACTH test, in which the subject receives 20 units over an eight-hour period (or 40 units over a four-hour period) by continuous infusion. Changes in circulating eosinophiles and urinary steroids are used as indices of response. Total absence of adrenal response is considered established only when such infusions have been repeated on three successive days without significant change. Although the intravenous ACTH test appears to be a relatively unequivocal method of detecting severely impaired adrenal cortex responsiveness, the required hospitalization makes it an expensive and inconvenient procedure.

40. (*a*) Wolfson, W. Q., and others: Corticogenic Hypothyroidism: Its Incidence, Clinical Significance and Management During Prolonged Treatment with ACTH or Cortisone, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2: Therapeutics, p. 95. (*b*) Robinson, W. D.: Discussion Following the Presentation by Drs. E. H. Venning, L. G. Johnson, and B. Rose, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2: Therapeutics, p. 63.

Since the intramuscular administration of 35 U. S. P. units of ACTX seems to provide an intensity of corticotropic stimulation approaching that of a 20 U. S. P. unit eight-hour ACTH infusion (Table 4), the possible usefulness of such ACTX doses as a replacement for the intravenous ACTH test has been studied.

Chart 9 indicates that blood eosinophile counts decrease continuously for at least the first eight hours after 35 units of ACTX in gelatin; that is, maximum eosinopenia does not occur before the eighth postadministration hour. The decrease in eosinophiles which obtains six hours after injection is, on the average, 88% of that observed eight hours after injection. A six-hour test interval has been chosen for routine use because the shorter period permits the test and its associated counts to be completed in a normal working day.

The results of a number of 35 U. S. P. unit, six-hour tests with long-acting ACTX are summarized in Chart 10. The first test dose given induced a median 90.5% decrease in eosinophiles in subjects with normal adrenal cortex responsiveness. It was rather surprising to find that an almost equally good response was given by 13 of the surgical patients who had not obtained a 50% eosinophile decrease on the conventional Thorn test or 8 unit aqueous ACTX test. These subjects showed a median 88% decrease in response to the first 35 unit test dose of long-acting ACTX.

When the 35 unit long-acting ACTX test was given to four rheumatoid arthritis patients after prolonged periods of continuous cortisone treatment, an entirely different response pattern was seen. None of these patients showed a significant six-hour eosinopenia on either the first or the second test day. Significant responses were observed on the third test day, but even then the median eosinopenic response did not approach that observed in normal subjects or in surgical patients hyporesponsive to 8 units of aqueous ACTH. Other reports have indicated that three days of eight hour intravenous ACTH infusions may be required to restore significant adrenal responsiveness after prolonged treatment with cortisone.

Chart 11 summarizes observations on a patient with psoriatic arthritis, in whom cortisone-induced adrenal unresponsiveness was overcome by the administration of 35 units of gelatin-ACTX on each of three successive days. Following this initial treatment, the use of gelatin-ACTX in doses of 20 to 35 units once every three or four days maintained satisfactory adrenal responsiveness despite the continued use of cortisone. However, in a second similar subject, adrenal unresponsiveness was not overcome during an initial trial of three daily 35 unit doses of gelatin-ACTX nor by the subsequent weekly administration of similar doses. There are increasing indications that operations, accidents, and other stresses may precipitate acute adrenal insufficiency with serious consequences not only when cortisone is withdrawn after prolonged treatment but, upon occasion, even when it is continued up to the occurrence of the added stress.[41] If adrenal responsiveness could be maintained by occasional use of single doses of long-acting ACTX, long-term use of oral cortisone would be much more physiological than at present. Our data would suggest that this desirable result can sometimes but not always be obtained and that additional study of its possibilities is most desirable.

41. (*a*) Roche, M.; Forsham, P. H.; Forsham, C. C., and Thorn, G. W.: A Study of Adrenal Cortical Response in Health and Diseases: The 48-Hour ACTH Test, J. Clin. Endocrinol. **10**:834, 1950. (*b*) Lewis, L.: Personal communciation to the author

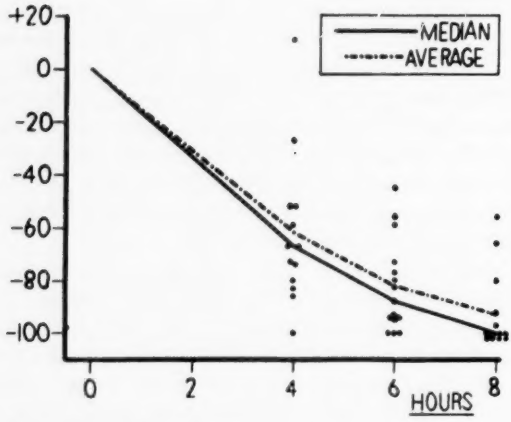


Chart 9.—Temporal characteristics of the eosinopenic response to 35 U. S. P. units of ACTX in gelatin. The 15 subjects whose responses were studied were surgical patients who had failed to show a 50% drop in blood eosinophiles four hours after either 25 U. S. P. units of aqueous ACTH or 8 U. S. P. units of aqueous ACTX. The vertical scale indicates per cent fall in eosinophiles.

Maximum eosinopenia following 35 U. S. P. units of long-acting ACTX is not achieved for at least eight hours. However, for convenience in planning the work of the laboratory, the six-hour response is studied unless maximum test sensitivity appears to be necessary. The response eight hours after administration is about 1.13 times as great as the six-hour response in the case of both median and average eosinopenia.

At the present time, the combination of an inadequate response to a small test dose of aqueous ACTH or ACTX plus an adequate response to a test with 35 U. S. P. units of long-acting ACTX does not appear to indicate a significant degree of adrenal cortex unresponsiveness, since the clinical response of such persons to stress is not impaired.

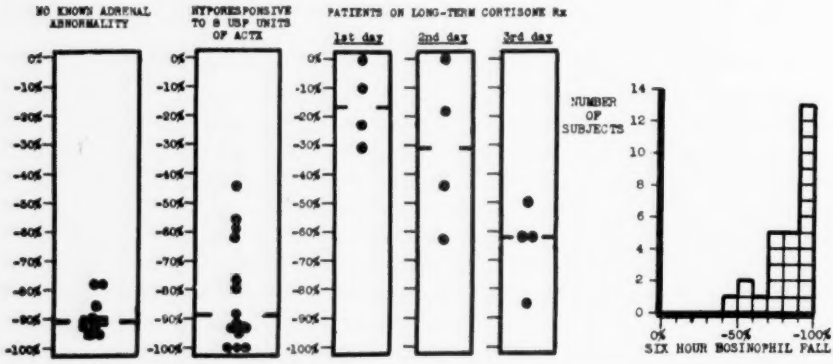


Chart 10.—Decrease in eosinophiles in the 35 U. S. P. unit, six-hour, intramuscular test with long-acting ACTX-corticotropin. The bar graph, on the right, shows the distribution of test results for normal subjects and for subjects hyporesponsive to 8 U. S. P. units of aqueous ACTX.

The results obtained in this preliminary study suggest that the intramuscular 35 U. S. P. unit, six-hour, long-acting ACTX test gives results similar to those of the intravenous ACTH test.

3. *Consistency of Estimates of Extravascular Potency of ACTX-Corticotropin Derived from Human Intramuscular Assay and from Animal Subcutaneous Assay in Blind Comparative Studies.*—One U. S. P. unit of an unknown corticotropin assayed according to the intravenous method of Sayers, Sayers, and Woodbury may represent an intramuscular potency from 25% to 300% of 1 unit of standard U. S. P. corticotropin given intramuscularly. If it is known that a particular unknown corticotropin is of the ACTX, ACTH, or ACTIDE type, this range is considerably narrowed. Unfortunately, during the manufacture of ACTX there have occurred losses of intramuscular potency without loss of intravenous potency,

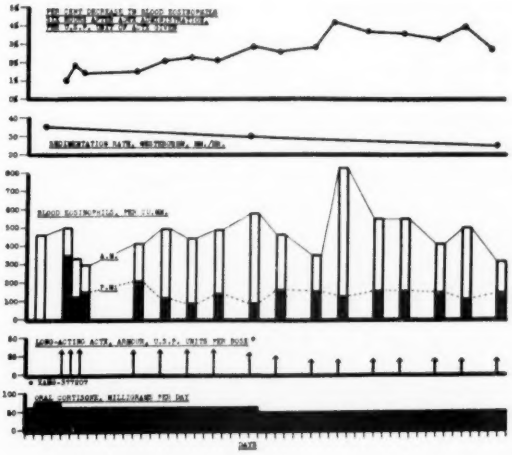


Chart 11.—Intermittent intramuscular long-acting ACTX in the restoration and maintenance of adrenal cortex responsiveness following prolonged continuous cortisone treatment.

The data are from Dr. C. B., a man with severe psoriatic arthritis, who, prior to the charted studies, had received suppressive dosages of cortisone continuously for more than six months.

The tall open bar in the third line of the chart shows the complete lack of eosinopenia following a 25 unit intramuscular dose of aqueous ACTH. The patient then received 35 U. S. P. units of ACTX-in-heavy-gelatin on each of three successive days. The morning (a. m.) counts before each dose and the afternoon (p. m.) counts six hours after each dose are shown in the third line of the chart. Thereafter, the patient received single doses of long-acting ACTX at intervals of from three to five days. That this resulted in a restoration of adrenal cortex responsiveness is indicated by the rising eosinophile depression per unit of administered ACTX, as shown in the upper line of the chart. It should be noted that adrenal cortex responsiveness continued to show a progressive increase for at least the first month of this treatment.

resulting in highly undesirable clinical consequences. It is apparent that when ACTX preparations intended for intramuscular use are assayed by an intravenous technique dependable predictions of intramuscular potency are not obtained.

The intramuscular potency of corticotropins can accurately be estimated in man by a number of techniques but all are far too time consuming for routine use if this can be avoided. Fisher and Thompson have therefore adapted the ascorbic-acid-

depletion method (Chart 1) and the more recently introduced thymus involution technique for the subcutaneous bioassay of corticotropin in the intact rat.[42]

Chart 12 compares results obtained by Fisher and Thompson using subcutaneous animal bioassay and by myself using human intramuscular bioassay techniques. The nine lots studied were compared on a blind basis, and results were not exchanged until both groups had completed their evaluation of the entire group of preparations. The coefficient of correlation between the two sets of estimates is +0.77. The three clinically unsatisfactory preparations mentioned earlier in this report had an average human bioassay of 45%% of expected potency and an average animal subcutaneous bioassay of 30% of expected potency. Six clinically satisfactory preparations had an average human bioassay equivalent to 114% of expected potency and an average animal subcutaneous bioassay equal to 132% of expected potency.

While there is good parallelism between animal and human extravascular assay in the case of gelatin and certain other water-miscible bases used for the pro-

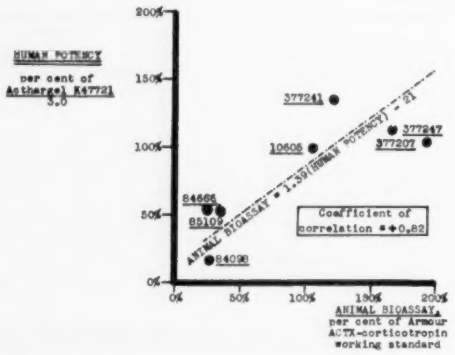


Chart 12.—Intramuscular bioassay of ACTX-corticotropins in man and in animals. The results illustrated were obtained in a blind comparative study. Animal bioassays were performed by Dr. Joseph D. Fisher. Human bioassays utilized the methods described in the text. Lots 84666, 85109, and 84098 were judged clinically unsatisfactory for use. Lots 10605, 377241, 377247, and 377207 appeared clinically satisfactory.

longation of corticotropin action, unpublished observations indicate that this parallelism may not obtain in the case of water-immiscible preparations. On subcutaneous administration in the intact rat, preparations of corticotropin in oil and aluminum monostearate appear to have considerably more favorable characteristics than when they are given to man by intramuscular injection. A plausible explanation for these differences is that such preparations remain as localized globules in the loose subcutaneous tissue of the rat, while in the much more tense subcutaneous tissue of man muscular action forcibly disperses them in tissue fluids. It seems advisable therefore to establish the existence of parallelism between human and animal extravascular assay for each new menstruum studied. In the case of gelatin preparations

42. Fisher, J. D., and Thompson, R. E.: A Proposed Ascorbic Acid Depletion Assay for ACTH, Which Correlates Clinical Effectiveness, J. Clin. Endocrinol. **12**:967, 1952. Fisher and Thompson.[15a]

this parallelism has been satisfactorily established, and the advisability of substituting subcutaneous animal assay for current intravenous bioassay methods seems clear.

4. *A Possible Qualitative Difference Between ACTX-Corticotropin and ACTH-Corticotropin.*—In some patients the daily dose of long-acting ACTX is followed within a few hours by a previously undescribed neurovascular syndrome, which rarely, if ever, follows therapeutically equivalent doses of long-acting ACTH. Most often, these unpleasant neurovascular changes reach maximum intensity about 6 to 12 hours after the daily dose of ACTX has been given. The unpleasantness of these reactions appears to be quite constant and may result in part from dizziness, giddiness, sensations of precordial or abdominal palpitation, irritability, or marked anxiety, which often accompany the more severe episodes. Clearly identical attacks have occurred in only one patient receiving long-acting ACTH and then only when she was somewhat overtreated. In this patient the real nature of these episodes was long unrecognized, and they were erroneously considered to be anxiety attacks until other patients had been given long-acting ACTX and similar symptoms had developed.

Objectively, the patient shows a ruddy flush which may be malar or more generalized. When generalized, the skin is warm and red and the superficial vessels refill rapidly after they are emptied by pressure. Increased sweating is noted by some but not all patients. The patient may report visual hallucinations, scintillating scotomata, or feelings of belligerence or fear generally recognized as disproportionate to environmental circumstances.

Many indications of increased cardiac output and peripheral vasodilatation are observed during severe attacks. There is generally sinus tachycardia accompanied by a wide pulse pressure. The latter most often has resulted from a large elevation in systolic pressure and a small rise in diastolic pressure. On the other hand, in one middle-aged woman with disseminated lupus erythematosus resting blood pressures were not unusual but during a neurovascular attack pressures of 145/0 to 160/0 consistently were recorded by independent observers. The thoracic and abdominal palpitation of which patients complain appears to be a subjective correlate of objectively palpable increased aortic pulsation. Classic signs of abnormally rapid run-off from the peripheral arterial tree have sometimes been seen, including such phenomena as head-nodding, capillary pulsation in finger nail beds, water-hammer pulse, and arterial "pistol-shot" sounds audible on auscultation over the antecubital space.

The frequency and intensity of neurovascular episodes is related to corticotropin dosage and may be increased or decreased by elevating or reducing daily dosage. Attacks were not abolished when the menstruum for long-acting ACTX was increased to the maximum viscosity which could be given through a No. 20 needle.

These neurovascular episodes are sufficiently frequent to constitute a real problem. Among our first 25 patients given definitive long-term treatment with long-acting ACTX, at least 6 patients had neurovascular reactions which required unusual efforts to adjust dosage very precisely to minimum therapeutic levels. This has not always been possible, and for some patients neurovascular reactions represent a continuing problem. The basic physiology of the disturbance is unclear. It appears to involve changes in central nervous function, peripheral arteriolar vasodilatation, and increased cardiac output. The transient changes in subjective

mood and cognition during these acute reactions seem unrelated to the sustained psychotic states sometimes seen during corticotropin treatment.

The frequency of such attacks after treatment with ACTX and their infrequency after ACTH cannot at present be assumed to be due to differences in the corticotropin molecules. It could also result from a removal of some protective component during the process of converting ACTH to ACTX. The timing of the attacks does suggest some relationship to circulating corticoid levels, since minimum eosinophile counts are generally found during attacks. (But it should be recalled that the eosinophile count reflects the corticoid level three or four hours before the count is taken.) Occasionally, oral cortisone-treated patients have shown suggestively similar reactions, particularly when the spacing of the daily dosage has favored a "piling-up" of cortisone effect at some time during the day.

Except for Lewis [41b] no workers have reported parallel observations under identical conditions. However, two reports on intravenous corticotropin infusions contain statements which suggest that the authors have noted similar phenomena. Renold and associates [7f] state, "A frequent observation was the early appearance of a generalized flush of the skin, sometimes accompanied by a subjective impression of warmth and often by sweating . . . most probably due to physiologic activity . . . did not represent an allergic phenomenon." Mandel and co-workers [7e] comment, "Common complaints during the first few hours of infusion were flushing of the face, a feeling of tightness across the chest and a sense of fullness in the abdomen."

Since only ACTX induces a significant frequency of neurovascular reactions when given at minimum therapeutic levels, its effects are clearly qualitatively different from those of ACTH. Because neither subtype is available in pure form, this qualitative difference may be found to reflect a difference in contaminants rather than in the corticotropin molecules. Inability to abolish these attacks has been a real problem in treating certain patients. On the other hand, the absence of reference to similar attacks in other publications suggests that other investigative groups have found these episodes less frequent or less impressive.

5. *Intramuscular Administration of Long-Acting ACTX on Multiple Daily Dose Schedules as a Means of Obtaining Maximum Therapeutic Effects.*—Physiologic Considerations: In studies on adrenal glands perfused in vitro, Hechter and his associates [43] have found that, for any given concentration of corticotropin in the perfusing fluid, there is a definitely limited rate at which the hormone can be fixed by the gland. When the corticotropin concentration of the perfusing fluid is increased, the total uptake of hormone per unit time also increases but to a lesser extent so that the percentage extraction falls. Because of this limited rate of fixation, if the perfusing blood is passed through the gland only once it may be necessary to use 100 units of corticotropin to achieve a degree of adrenal activation which could be produced by recirculating blood containing 1 unit of corticotropin for an hour.

The practical importance of this fall in percentage extraction by the adrenal with increasing corticotropin concentration is to be found from a consideration of the in vivo fate of corticotropin. The biological half-life of corticotropin in the blood stream is only 5 to 10 minutes, unlike other plasma proteins, which have

43. Hechter, O.: Discussion of Presentation by Dr. Peter H. Forsham, in Proceedings of the Third Clinical ACTH Conference, Chicago, The Armour Laboratories, 1952, p. 135.

half-lives of one or more days.[44a] This rapid removal of corticotropin appears largely to be the result of removal by the kidneys, and, so far as is now known, hormone once removed from the blood stream is thereafter ineffective. In addition, these extra-adrenal corticotropin-removing systems appear not to saturate easily as corticotropin concentrations increase. In other words, the adrenal cortex must compete with other tissues for circulating corticotropin, and, because of the falling extraction at higher levels, an increased blood corticotropin concentration will result in a larger percentage of hormone being diverted to fixation at extra-adrenal sites.

In practical terms, these considerations mean that the wastage of corticotropin will be greater at high blood levels than at low blood levels. Thus, if the therapist wishes to obtain the maximum possible adrenal stimulation from a particular amount of corticotropin, he will give it intravenously (to avoid extravascular inactivation) and he will arrange his infusion to run at the slowest practical rate, in order to take advantage of the more favorable relation between adrenal and extra-adrenal fixation which obtains at low blood levels. Two limiting factors must be considered. If the infusion runs too slowly, the degree of adrenal stimulation will be insufficient. In addition, breakdown of the corticotropin may occur in the infusion bottle.

If the treatment problem were merely that of obtaining the greatest adrenal stimulation from the least corticotropin, continuous intravenous infusions would be ideal. Under real conditions, however, it may be considerably more important to avoid the discomfort and immobilization required by such infusions. The therapist may therefore elect to attempt to approach optimal conditions by using ACTX, a corticotropin which undergoes little extravascular inactivation and by incorporating the hormone into a retarding menstruum. Because of its very short biological half-life, anything which effects an appreciable delay in the entrance of corticotropin into the circulation will appear to cause a considerable increase in effectiveness. Thus, incorporation of corticotropin into 16% gelatin, a relatively ineffective retarding agent, results in a preparation which is twice as effective as aqueous corticotropin when both materials are given intramuscularly on the same time schedule.[6]

The short biological half-life of circulating corticotropin and the unfavorable ratio of adrenal to extra-adrenal fixation which obtains at high blood levels explains the great importance of giving multiple daily doses when using intramuscular aqueous corticotropin. Mote [44b] estimated that if aqueous ACTH were given only once every 24 hours the daily dose required would be more than five times as great as that required when the hormone was given every 6 hours. Obviously, the more effective the depot action of a long-acting menstruum, the more closely will the effects of a single daily dose approach those of the six-hour schedule. However, even if the best available long-acting menstrua are used, approximately twice as much corticotropin must be used if a single daily dose is given rather than four doses at six-hour intervals.[46]

44. (*a*) Richards, J. B., and Sayers, G.: Fate and Excretion of Adrenocorticotrophic Hormone, Proc. Soc. Exper. Biol. & Med. **77**:87, 1951. (*b*) Mote, J. R.: General Principles to be Considered and Directions for Using ACTH (Armour), Chicago, The Armour Laboratories, 1950, p. 27.

45. Footnote deleted.

46. Wolfson.[14b] Wolfson.[28a]

Chart 13 summarizes data which emphasize the relative inefficiency of giving a single daily dose of ACTX in 16% gelatin. In this study, a single 100 unit dose of gelatin-ACTX was shown, in two normal adults, to produce an increase in 24-hour 17-ketosteroid excretion which was indistinguishable from that produced by giving three 10 unit doses of the same gelatin-ACTX at eight-hour intervals. In other words, even though a 16% gelatin menstruum will double the apparent effectiveness of aqueous corticotropin, single daily doses of corticotropin in this base are only about one-third as efficient as three daily doses. As already has been mentioned, no currently available long-acting menstruum is able to delay corticotropin absorption enough to achieve approximate equality of effects between single daily doses and multiple dosage schedules.

Clinical Observations: Two considerations make possible the a priori prediction that when both are given intramuscularly at six-hour intervals one U. S. P. unit

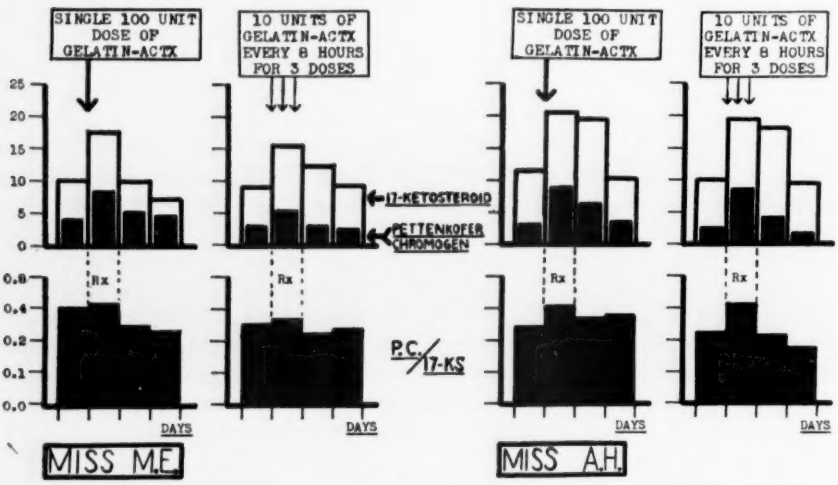


Chart 13.—Increase of the apparent effectiveness of long-acting ACTX by use of multiple daily injections. Approximately equal increases in daily 17-ketosteroid output produced in two normal subjects by a single, 100 U. S. P. unit dose of ACTX in 16% gelatin and by 30 U. S. P. units of the same material given in three 10 unit doses at eight-hour intervals.

of ACTX in 16% gelatin will produce effects equivalent to those produced by 6 or more U. S. P. units of aqueous ACTH: (1) an apparent doubling of potency is achieved by incorporating any corticotropin in 16% gelatin, and (2) when given intramuscularly as an aqueous solution, each unit of ACTX is physiologically equivalent to three or more units of ACTH. The study of Chart 7 actually represents a test of this prediction. The finding that gelatin-ACTX given intramuscularly every six hours was 6.6 to 8.2 times as effective as aqueous ACTH given on the same schedule represents a satisfactory confirmation of the theoretical calculations.

Charts 14 and 15 are representative examples of the intense physiological effects seen in patients given four daily doses of intramuscular gelatin-ACTX. The two eye patients of Chart 14 failed to show any clinical improvement or notable

metabolic effect when given 125 to 150 mg. of cortisone daily. The metabolic, hematologic, and therapeutic effects induced by 10 to 15 units of gelatin-ACTX given every six hours far exceeded those of the cortisone given previously. Moreover, these effects were maintained by 5 units of gelatin-ACTX every six hours.

Chart 15 summarizes similar observations in three additional eye patients. Mrs. R. M., a patient with chronic retinitis pigmentosa, had no immediate clinical improvement but did manifest a marked weight gain, leucocytosis to 30,000 per cubic millimeter, and complete disappearance of circulating eosinophiles on 5 units of gelatin-ACTX every six hours. A similar dosage of 20 units per day of gelatin-ACTX elicited rapid improvement in the other two patients. Both of these had eye diseases in the category which Quinn and Wolfson [33] had previously shown to require a median daily dosage of 115 units of long-acting ACTH given once daily in order to establish definite improvement.

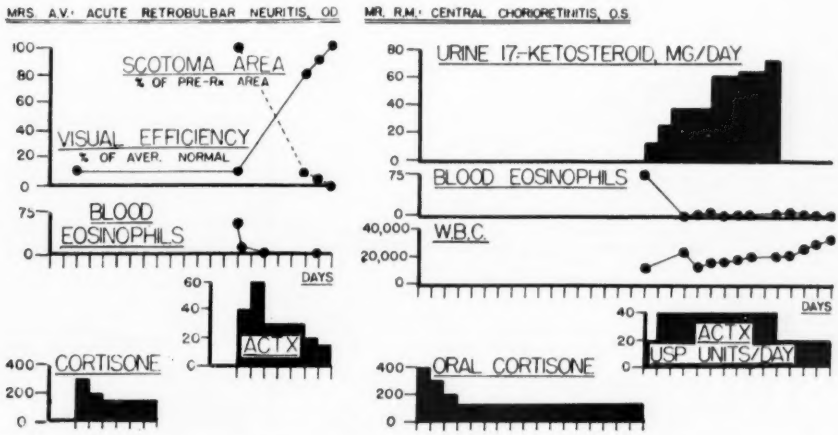


Chart 14.—Therapeutic, hematologic, and metabolic effects of ACTX in 16% gelatin given intramuscularly every six hours.

These clinical findings are consistent with the calculated prediction that approximately 16 U. S. P. units per day of gelatin-ACTX (4 units intramuscularly every six hours) would duplicate the physiological effects of 100 U. S. P. units per day of aqueous ACTH (25 units intramuscularly every six hours). A number of investigators have confirmed Gordon's original report that 10 to 20 U. S. P. units of ACTH, infused intravenously daily over an eight-hour period, also would duplicate the effects of 100 units per day of intramuscular aqueous ACTH.[7] From these two sets of findings it appears that identical effects can be obtained from a particular unitage of ACTX (or ACTH) given by continuous intravenous infusion for eight hours each day or from the same unitage of gelatin-ACTX given in quarter-doses intramuscularly every six hours.

I strongly believe that, with a single exception, continuous intravenous infusions of corticotropin have no legitimate role in current therapeutics. The equivalence of effects produced by the eight-hour infusion and by multiple-dose gelatin-ACTX schedules even deprives this procedure of the virtue of economy, which was its chief original justification. In fact, since each intravenous infusion requires fresh sterile equipment and since patients ordinarily must be hospitalized, the use of

infusions actually is a relatively expensive procedure. At University Hospital increasing resistance by both the patients and the house staff have generally made it necessary to discontinue infusions after four or five days. A considerable percentage of infusions are not completed on schedule because of technical interruptions. At a time when it is particularly desirable that patients take full advantage of the anabolic effects of activity, intravenous corticotropin infusions add the markedly catabolic effect of bed rest to that of a fundamentally catabolic (or antianabolic) hormone. Serious allergic accidents have already occurred when intravenous infusions were given to patients with unresponsive adrenals. None has yet been reported in a patient hypersensitive to crude ACTH because of previous administration of the hormone (or of hog liver extract), but it would certainly

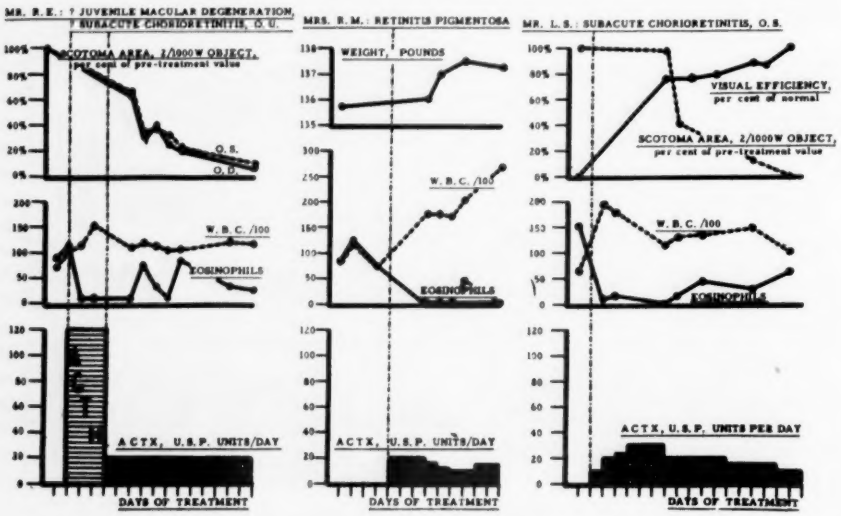

MR. R. E.: ? JUVENILE MACULAR DEGENERATION, ? SUBACUTE CHORIORETINITIS, O. U.
SCOTOMA AREA, 2/1000 W OBJECT, per cent of pre-treatment value
O. S.
O. D.
W. B. C. /100
EOSINOPHILS
ACTX, U. S. P. UNITS/DAY
DAYS OF TREATMENT
MRS. R. M.: RETINITIS PIGMENTOSA
WEIGHT, POUNDS
W. B. C. /100
EOSINOPHILS
ACTX, U. S. P. UNITS/DAY
DAYS OF TREATMENT
MR. L. S.: SUBACUTE CHORIORETINITIS, O. S.
VISUAL EFFICIENCY, per cent of normal
SCOTOMA AREA, 2/1000 W OBJECT, per cent of pre-treatment value
W. B. C. /100
EOSINOPHILS
ACTX, U. S. P. UNITS PER DAY
DAYS OF TREATMENT

Chart 15.—Therapeutic and hematologic effects of ACTX in 16% gelatin given intramuscularly every six hours.

seem unwise to regard this as indicating that corticotropin may safely be given intravenously to sensitive patients. There is, in fact, no satisfactory reason for considering corticotropin an exception to the general principle that because proteins are generally antigenic their intravenous administration is inadvisable if it can be avoided and their repeated intravenous administration at widely spaced intervals is most strongly contraindicated.

Intravenous administration of corticotropin has been helpful in treating intramuscular refractoriness to crude ACTH. However, present data suggest that ACTX seldom causes intramuscular refractoriness and that patients refractory to intramuscular ACTH may continue to respond to intramuscular ACTX. Conceivably an occasional patient may become unresponsive to intramuscular ACTX, and, in this event, intravenous infusions would be entirely justifiable. However, when the actual goal is maximum corticotropic stimulation at minimum cost, intramuscular administration of gelatin-ACTX in divided daily doses appears to be the technique of choice.

COMMENT

1. *Basic Biochemistry, Physiology, and Pharmacology of the Corticotropin Subtypes.*—Table 4 attempts to present equally effective dosage schedules for the three corticotropin subtypes given by different routes, in different menstrua, and at different time intervals. From this table one may infer that (1) 1 U. S. P. unit of any subtype provides identical adrenal stimulation when given by intravenous infusion over a particular period and (2) when corticotropins are given intramuscularly in gelatin every six hours, a total daily dose of 2 U. S. P. units of ACTX, 6.25 U. S. P. units of ACTH, or 25 U. S. P. units of ACTIDE must be given to reproduce the effect of a 1 unit, 24-hour, intravenous infusion. It is apparent that almost all of the ACTIDE, most of the ACTH, and a relatively small fraction of the ACTX is inactivated in the extravascular tissues and never reaches the blood stream. Thus, the major difference between the three corticotropin subtypes is in their differential susceptibility to extravascular inactivation.

Possible Qualitative Differences Between Subtypes: ACTX and ACTH show no differences in their interaction with gelatin menstrua, since potency ratios obtained with gelatin preparations closely parallel those obtained with aqueous solutions. They also show close parallelism in their ability to induce therapeutic, hematologic, or metabolic effects. However, a certain proportion of well-stabilized patients, when transferred from long-acting ACTH to long-acting ACTX in therapeutically equal dosage, report a characteristic and unpleasant neurovascular syndrome, which occurs in the first few hours after each injection. Until it is possible to undertake studies with pure ACTH and pure ACTX, it will not be permissible to regard the different frequency of neurovascular reactions as arising from differences in the corticotropin molecules themselves. Such a difference might equally well arise from the removal of a contaminant present in crude ACTH.

Are the Corticotropin Subtypes Chemically Specific? In the normal adult most of the intramuscularly administered ACTH is inactivated extravascularly. Some subjects given ACTH repeatedly show progressive heightening of this extravascular inactivation. This would indicate that the inactivation of intramuscularly administered ACTH must be regarded as due to the operation of a special enzymatic EVIS (extravascular-inactivating-system).

In certain subjects even extremely large doses of intramuscular ACTH are ineffective, despite the continued effectiveness of intravenous infusions; in other words, EVIS activity has increased until 100% of the administered ACTH is being inactivated. For this to occur it is obviously necessary to assume that all of the ACTH is EVIS-susceptible.

A patient who is completely refractory to intramuscular ACTH may, nevertheless, respond normally to ACTX. For this to occur, obviously most of the ACTX must escape extravascular inactivation; that is, most ACTX is EVIS-resistant. If virtually all ACTH is EVIS-susceptible and most ACTX is EVIS-resistant, ACTX and ACTH are probably chemically distinct substances.

Improbable alternative hypotheses have been proposed. Because ACTIDE, which certainly has no carrier protein, is even more EVIS-susceptible than ACTH, it is unlikely that any properties of a protein carrier explain EVIS-susceptibility. The greater EVIS-susceptibility of ACTIDE is also strong evidence against an important participation of proteolytic enzymes or of co-factors which activate tissue

TABLE 4.—*Corticotropin Schedules Physiologically Equivalent to 100 U. S. P. Units per Day of Intramuscular ACTH-Corticotropin Administered in Four Equal Doses at Six-Hour Intervals: Effect of Changes in Hormone Subtype, Menstruum, and Administration Route upon Daily Corticotropin Requirements*

Dosage Schedule	Aqueous ACTH U. S. P. Units/Day	ACTH in Gelatin * U. S. P. Units/Day	ACTX in Gelatin * U. S. P. Units/Day	Aqueous ACTIDE U. S. P. Units/Day
Intermittent intramuscular administration				
One-fourth of the daily dose every 6 hr.	100	50 (Light gelatin) †	16 (Light gelatin) ‡	400 §
One-half of the daily dose every 12 hr.	No data	93 (Heavy gelatin) ‖ 121 (Light gelatin)	29 (Heavy gelatin) ‖ 38 (Light gelatin)	No data
Entire daily dose once each day	Over 200 ¶	116 (Heavy gelatin) ⁋ 151 (Light gelatin) **	36 (Heavy gelatin) †† 47 (Light gelatin) ‡‡	No data
Intravenous administration				
One 8-hr. infusion each day	15 §§	15 ‖‖	15 ‖‖	15 ¶¶
One 24-hr. infusion each day	7.5 ⁋⁋	7.5	7.5	7.5
Estimated percentage of hormone which undergoes extravascular inactivation				
Maximum estimate ***	85	85	50	96
Minimum estimate ***	70	70	0	93

* Light gelatin preparations become liquid after being held briefly in the hand and may be administered through a No. 23 needle; they contain from 15 to 24% gelatin. Heavy gelatin preparations require warming under a hot water tap before they can be given through a No. 21 needle; they contain from 25 to 33% gelatin.

† Unpublished studies in this laboratory [6] confirm the claim of Landa Bacallao [84] that substitution of ACTH in light gelatin every six hours intramuscularly for aqueous ACTH every six hours intramuscularly approximately halves the daily requirement.

‡ From Table 2, on the average, each U. S. P. unit of ACTX is physiologically equivalent to 3.2 U. S. P. units of ACTH when both are given in the same menstruum and on the same time schedule. The inference that gelatin-ACTX every six hours intramuscularly is more than six times as effective per U. S. P. unit than aqueous ACTH every six hours intramuscularly is supported by the data of Chart 7, which shows such a comparison. The Table shows intramuscular administration of gelatin-ACTX every six hours to require only one-third of the daily ration needed for intramuscular administration every 24 hours of the same preparation. Chart 12 establishes this relationship.

§ Per U. S. P. unit, intramuscular ACTIDE is only 25% as effective as intramuscular ACTH.[5] Because of the unpromising characteristics of ACTIDE, it has received only limited study in the clinic. This figure should therefore be considered a first approximation.

‖ When long-acting corticotropins are given every 12 hours rather than once daily, the daily dose requirement is reduced approximately 20%.[28a]

¶ In an early summary of clinical studies on ACTH, Mote has written, "[giving] the total daily dose of [aqueous] ACTH in a single injection has resulted in no appreciable change in the clinical status of most patients even when as much as 200 mg. per injection was administered."

⁋ From 24-hour eosinopenia data (Table 1) and the dose : response curve for Adactar, ACTH in heavy gelatin is approximately 86% as effective as Adactar prepared from isoelectric precipitated ACTH. A single daily dose of 100 units of Adactar will ordinarily replace 100 units of aqueous ACTH given every six hours intramuscularly. The same activity will be exhibited by 116 (i. e. 100/0.86) units of ACTH in heavy gelatin given once daily.

** From Table 2, it appears necessary to give 1.3 units of corticotropin in light gelatin to reproduce the effects of 1.0 units of the same hormone preparation in heavy gelatin. A second and somewhat larger estimate can be obtained from the 24-hour eosinopenia data of Table 1. The former value is consistent with clinical experience and has therefore been used rather than the latter, which appears somewhat too large.

†† On the average, per U. S. P. unit, intramuscular ACTX is 3.2 times as effective as intramuscular ACTH (Table 2).

‡‡ On the average, it requires 1.3 units of ACTX in light gelatin to reproduce the effects of 1.0 unit of ACTX in heavy gelatin (Table 2).

§§ When ACTH is given intravenously in a daily eight-hour infusion, each unit appears physiologically equivalent to between 5 and 10 units of aqueous ACTH given intramuscularly every six hours and daily corticotropin requirements are only 10 to 20% as large as for intermittent intramuscular injection of aqueous ACTH.[7]

‖‖ Identical log dose : response relationships are obtained when hog ACTH, beef ACTH, sheep ACTH, hog ACTX, and beef ACTX are given by continuous intravenous infusion over similar time periods (Renold;[7f] Jenkins [16]).

¶¶ Per U. S. P. unit, intravenous infusions of ACTIDE and ACTH appeared to produce identical effects when given over the same time interval.[5]

⁋⁋ When ACTH is given by continuous intravenous infusion for a 24-hour period each day, each unit appears 10 to 20 times as effective as aqueous ACTH given intramuscularly every six hours.[7c, f]

*** Estimates of the minimum extravascular destruction of corticotropins are based upon the assumption that intramuscular administration every six hours is not as intrinsically efficient a schedule as continuous intramuscular infusion. The latter type of administration was not used in our studies but has been studied by Jenkins,[16] who finds intramuscular and intravenous infusions of ACTX closely comparable. Estimates of the maximum extravascular destruction are based on the assumption that the entire difference between a continuous 24-hour intravenous infusion and intramuscular administration every 6 hours of gelatin preparations represents the effect of the extravascular inactivating system. The bulk of present evidence suggests that the minimum estimates may represent the closer approximation.

proteases. A highly purified ACTX preparation may, by suitable operations, be converted either to material with characteristic ACTH or to material with characteristic ACTIDE properties. The necessary manipulations are such as to make a possible introduction of proteolytic enzymes impossible and introduction of co-factors extremely improbable.

All three corticotropin subtypes have been prepared from hog, beef, and sheep pituitary. It has also been shown that in the rat, as in man, most of the extravascularly administered ACTH and an even greater proportion of ACTIDE are inactivated. Thus, there is suggestive evidence that the potential existence of three corticotropin subtypes which differ in EVIS-susceptibility may be a general physiological property.

Most of the ACTX preparations currently available have been prepared by the process of glacial acetic acid extraction and subsequent fractionation on oxycellulose, which was developed in Dr. Astwood's laboratory. This process will not work properly unless the pretreatment with glacial acetic acid or related substances has been carried out, suggesting that a critical step occurs prior to fractionation. In addition, at least two manufacturers have prepared crude ACTX-corticotropins which exhibit intramuscular activity per unit which is approximately three times that of intramuscularly administered U. S. P. ACTH-corticotropin per unit. (Unless the present provisional terminology is altered, these materials will have to be referred to as "crude corticotropin purified," a hopeless absurdity.)

Use of ACTX in Intramuscular Tests of Adrenal Cortex Function: The four-hour eosinopenic response following the intramuscular injection of 8 U. S. P. units of aqueous ACTX is not statistically significantly different from that following 25 U. S. P. units of aqueous ACTH in similar subjects. It is highly significantly different from the response to 12.5 U. S. P. units of aqueous ACTH.

Fifteen subjects who had failed to show a 50% drop in eosinophiles four hours after either 8 units of aqueous ACTX or 25 units of aqueous ACTH received 35 U. S. P. units of ACTX in gelatin. Eosinophile counts fell progressively for the eight-hour observation period. At the eighth hour, eight subjects had a 100% drop in eosinophiles, three subjects had an 80 to 99% drop, and two subjects had a 50 to 79% drop. (No eight-hour count was performed in two subjects.)

For purposes of working convenience, we have suggested study of the six-hour eosinopenic response to the intramuscular injection of 35 U. S. P. units of ACTX in gelatin. Six-hour eosinopenia was greater than 75% in all of 10 normal subjects and in 11 of 15 persons who had not shown a satisfactory response to the smaller test dose. Of these 25 subjects, all but one had a better than 50% six-hour eosinopenia. Restoration of adrenal cortex responsiveness after long-term cortisone therapy by administration of daily 35 U. S. P. unit doses of gelatin-ACTX for three days has also been shown.

From the available data, the eosinopenic response to the 8 U. S. P. unit four-hour, intramuscular, aqueous ACTX test is indistinguishable from the response to the usual Thorn test, and these procedures appear interchangeable. The 35 U. S. P. unit, six-hour, intramuscular, gelatin-ACTX test gives results similar to those of the present intravenous ACTH test. Whether the two may be considered identical must await studies of steroid excretion now in progress. When maximum sensitivity is desired, the eosinopenic response eight hours after giving the gelatin-ACTX should be observed, since this is regularly appreciably greater.

2. *The Bioassay, Standardization, and Labeling of ACTX-Corticotropins.*—The introduction of ACTX into clinical use is a *fait accompli* which, on the whole, has been accomplished with only minimal confusion to the practicing physician, because of the cooperative efforts of the United States Pharmacopeia, the Food and Drug Administration, the manufacturers of corticotropin, and the cooperating investigators.

If the labels of ACTX preparations had carried the designation "corticotropin" only (as with ACTH preparations) and the unitage determined by intravenous assay, the results might have been disastrous. Two preparations bearing the same name and same unitage but differing three-fold in potency would simultaneously have been available.

Present Procedure: ACTX-corticotropins were given the distinguishing generic name of "corticotropin, purified," while the older ACTH-corticotropin was designated "corticotropin, crude." "Corticotropin, purified" was labeled in physiological units which were intended to produce the same intramuscular effect as a U. S. P. unit of "corticotropin, crude" but which actually were ⅓ of a U. S. P. unit.

It next became necessary to set up procedures for distinguishing a "purified" preparation which was to be labeled in physiological units from a "crude" preparation to be labeled in U. S. P. units. In practice, the following steps appear to have been used: 1. When a manufacturer believes that his corticotropin has ACTX properties, he may attempt to demonstrate by human assay procedures that each U. S. P. unit, given intramuscularly, produces physiological changes equivalent to those of 3 U. S. P. units of U. S. P. corticotropin given intramuscularly in a comparable menstruum and on a comparable schedule. 2. If these first human studies bear out the original impression of ACTX characteristics, more exact studies are undertaken. Various clinical investigators receive samples which have been exhaustively assayed by the intravenous method. Using human assay procedures of their own choice, the investigators estimate the apparent intramuscular effectiveness of the ACTX in comparison with a standard ACTH preparation. If it is found that 1 U. S. P. unit of the manufacturer's ACTX is equivalent to 3.3 U. S. P. units of ACTH when both are given intramuscularly under standard conditions, the manufacturer's ACTX is reported to have a 3.3. potency ratio. 3. If the various investigators show adequate agreement and potency ratios appear consistent from lot to lot, it will be possible to select an average potency ratio which is characteristic of the product resulting from a particular process. In the statement filed with the Food and Drug Administration, the material is described as a "corticotropin, purified" prepared by a stipulated process with a stipulated potency ratio. 4. The stipulated potency ratio may now be used as a basis for labeling so long as manufacturing technique is unchanged. If, for example, the XYZ Company has established a potency ratio of 3.2 for their preliminary runs of "corticotropin, purified," this need no longer be checked, once the product is approved. Instead, they subsequently may assay their production runs of ACTX by the intravenous procedure and then multiply the concentration in U. S. P. units by 3.2 to obtain the concentration in physiological units.

If the stability of the potency ratio really were dependable, this would have been a satisfactory procedure. Instead, subtle changes in manufacturing resulted in preparations with considerably less than half of the expected intramuscular potency in the case of three lots used in this study. However, because these lots

retained their expected intravenous potency, their defective nature went undetected by the manufacturer. A consideration of this experience will show that the present method of establishing potency actually contains no safeguard against a loss of intramuscular potency without a loss of intravenous potency.

Suggested Procedure: The calculation of potency by multiplying intravenous bioassay potency by a fixed multiplier must be abandoned as being dangerously unreliable. Corticotropins must be assayed by techniques which actually parallel clinical intramuscular potency. Human bioassay is theoretically practical but actually so cumbersome as to be highly undesirable if a reasonably adequate alternative exists. The subcutaneous rat bioassay methods developed by Fisher and Thompson appear attractive, and data summarized earlier in this report show that their results have a high positive correlation with the results of human bioassay, at least in the case of corticotropins in gelatin. Until this is completely validated, it is suggested that both the older technique and the subcutaneous animal assay be used to estimate potency and that preparations be released only when the two values are consistent.

3. *The Practical Advantages and Limitations of ACTX-Corticotropin.*—ACTX has five definite advantages over ACTH. Because its manufacture permits roughly three times as much intramuscular activity to be prepared from a given weight of pituitary, the cost per unit of activity is appreciably reduced. ACTX apparently has not led to specific intramuscular refractoriness, and subjects with intramuscular refractoriness due to previous ACTH treatment may respond normally to intramuscular ACTX from the same species. For the same reason, ACTX is a more desirable material for intramuscular tests of adrenal cortex function, particularly if the subjects previously have received ACTH. Finally, no more U. S. P. units are required when gelatin-ACTX is given every six hours intramuscularly than when ACTH is given in a single daily eight-hour intravenous infusion. However, the true cost of the intermittent intramuscular gelatin-ACTX treatment may be very considerably less, because sterile equipment for intravenous infusion, trained attendants, and hospitalization are not required.

Although these are real advantages, they should not mask the failure of ACTX-corticotropin to solve certain of the central problems of corticotropin treatment. The safe range between inadequate treatment and hypercorticoidism, narrow at best and often absent, is not significantly widened by substitution of ACTX for ACTH. Indeed, it is somewhat narrowed in those patients who show troublesome neurovascular reactions with ACTX but not with ACTH. Above all, ACTX has not assisted in the solution of the major therapeutic problem, that of eliminating the undesirable effects of the therapeutically active adrenal steroids without interfering with their extensive and dramatic ability to control disease. The best which can be expected from further purification of the corticotropins now available is that with rigidly standardized preparations some closer adjustment of dosage to individual requirements will be possible.

Reduced to the simplest terms, ACTX does not increase, and sometimes even decreases, the possibility of giving a therapeutically effective hormone dosage without causing hypercorticoid manifestations. On the other hand, it does reduce the cost of treatment and considerably increases the assurance that treatment may be continued for prolonged periods, with interruptions if desired, without the development of intramuscular refractoriness when the hormonal action is most seriously needed.

SUMMARY

Three subtypes of corticotropin may be differentiated. Each possesses a characteristic liability to inactivation when given intramuscularly or subcutaneously, at least in the rat and in man. The sense of present evidence, although largely inferential, strongly suggests that these subtypes are chemically distinct substances.

At least 67% of intramuscularly administered ACTH-corticotropin (U. S. P. corticotropin, "corticotropin, crude") undergoes extravascular inactivation in a previously untreated subject, and, following repeated courses, some subjects develop a specific ability to inactivate virtually all ACTH given extravascularly while remaining sensitive to intravenous ACTH. ACTIDE-corticotropin is even more susceptible to extravascular inactivation, less than 10% reaching the blood stream after intramuscular administration. However, little or no ACTX-corticotropin ("corticotropin, purified") is inactivated when this subtype is given by an extravascular route. It has been reported that subjects do not become refractory to extravascular ACTX and that patients who are unresponsive to intramuscular ACTH may continue to respond normally to intramuscular ACTX from the same species.

Commercial ACTX-corticotropins at present are labeled intramuscular "physiological units." This unitage is determined by an indirect procedure, in which animal intravenous potency is multiplied by a predetermined and fixed potency ratio. This is not a satisfactory procedure. Certain ACTX preparations have, during processing, lost much of their intramuscular effectiveness without significant loss in apparent intravenous potency. The only satisfactory method of establishing potency is its estimation by an animal extravascular assay which parallels human intramuscular effectiveness. Blind comparative studies have indicated good parallelism between human intramuscular potencies as obtained by the methods of the present report and recently developed animal extravascular bioassay procedures introduced by J. D. Fisher and R. E. Thompson.

The possible existence of qualitative differences between the effects of ACTH-corticotropin and ACTX-corticotropin has received considerable study. It has been found that each U. S. P. unit of intramuscularly administered ACTX produces therapeutic, metabolic, and hematologic effects in man equivalent, on the average, to those of between 3.19 and 3.46 U. S. P. units of intramuscular ACTH. These ratios obtain, naturally, only if both preparations are given in comparable menstrua and with comparable intervals between individual doses. The similarity of the ratios for different actions suggests little qualitative difference between ACTH and ACTX. On the other hand, when therapeutically equivalent dosages are given, ACTX frequently produces an unpleasant neurovascular syndrome in the first few hours after administration, while ACTH seldom induces similar changes. Until pure ACTX and pure ACTH can be compared, these differences may not be considered to result from differences in the corticotropin molecules themselves. Removal of a contaminant from ACTH might account for the higher frequency of reactions after ACTX.

Approximately three times as much corticotropin activity is obtained when ACTX-corticotropin rather than ACTH-corticotropin is prepared from a given weight of pituitary. This has already resulted in a substantial decrease in the cost of corticotropin treatment and seems destined, in the relatively near future, to lead to the disappearance of ACTH-corticotropin from commercial markets.

The development of adrenal cortex function tests utilizing ACTX-corticotropin has appeared important because ACTH may not continue to be available; because variable intramuscular inactivation limits the usefulness of intramuscular ACTH tests, particularly in subjects who have previously received this subtype, and because of the cumbersomeness of the intravenous ACTH tests suggested as a means of bypassing intramuscular ACTH tests. A four-hour intramuscular test employing 8 U. S. P. units (25 physiological units) of aqueous ACTX produces eosinopenic responses statistically indistinguishable from the responses to the 25 U. S. P. units of aqueous ACTH used in the original Thorn test. A six-hour intramuscular test with 35 U. S. P. units (100 physiological units) of long-acting ACTX seems a promising potential substitute for current test procedures which utilize intravenous ACTH infusions.

ACTX-corticotropins have distinct advantages over the earlier ACTH- corticotropins. The cost of each unit of intramuscular corticotropic activity is reduced. Danger of intramuscular refractoriness appears to be slight, and this offers obvious advantages in both treatment and testing of patients. The much smaller amounts of protein given when ACTX is used probably reduce the likelihood of acquired sensitivity. Finally, ACTX in gelatin given intramuscularly every six hours appears to produce physiological effects comparable to those of the same number of U. S. P. units given in a daily eight-hour infusion intravenously, but with considerably less cost and inconvenience than the intravenous infusions. On the other hand, ACTX does not increase the frequency with which a therapeutically adequate dosage of corticotropin may be given without inducing undesirable hypercorticoid manifestations, nor is it likely that this result will be achieved by further purification of the presently available corticotropin subtypes.

It is strongly recommended that the present provisional nomenclature adopted for the labeling of corticotropin subtypes be replaced. In their concentration of units per milligram, ACTX-corticotropins designated "purified" at present may be indistinguishable from ACTH-corticotropin. Suitable manipulation of an ACTX- corticotropin may produce a product indistinguishable from ACTH-corticotropin and without any change in the degree of purification, yet the former is designated "purified" and the latter "crude." A second change essential for safety appears to be the substitution of a satisfactory animal extravascular assay for the procedure now employed in determining the intramuscular potency of preparations of ACTX-corticotropin.

ADDENDUM

Biochemical evidence increasingly supports the physiological differentiation of adrenocorticotropin into three subtypes. W. F. White and W. Fierce [47] have differentiated three active corticotropin subtypes by chromatography on XE97 resin. The isolation of corticotropin B, which corresponds to the ACTIDE-corticotropin of this report, has been noted by N. G. Brink and his associates.[48] The isolation of corticotropin A, which corresponds to the ACTX-corticotropin of this report, has been reported by W. F. White.[49]

47. White, W. F., and Fierce, W.: J. Am. Chem. Soc. **75**:245, 1953.

48. Brink, N. G., and others: J. Am. Chem. Soc. **74**:2120, 1952.

49. White, W. F.: J. Am. Chem. Soc. **75**:503, 1953.

Case Reports

DRAINAGE OF PULMONARY VEINS INTO DUCTUS VENOSUS WITH OTHER ANOMALIES

HENRY D. SPECHT, M.D.
AND
A. F. BROWN, M.D.
GLENDALE, CALIF.

ANOMALOUS drainage of the pulmonary vessels is not very common, although Hughes and Rumore,[1] in a series of autopsies, found an incidence of 0.7%. Brody [2] reviewed the literature in 1942 and found 102 cases, to which he added 4 of his own. He divided these cases into those representing complete drainage of the pulmonary veins into the right atrium or its tributaries and those with incomplete drainage of the pulmonary veins into the right atrium or its tributaries. He reported 38 cases belonging to the first group. Incomplete drainage is not incompatible with long life; in fact, Brody states that 35 of the patients he reported lived to adulthood. However, of that group having complete drainage of pulmonary blood into the right atrium only eight lived beyond six months and the oldest lived to be 27 years of age. It has been stated that if less than 50% of the pulmonary venous return is to the right atrium there is little likelihood of decompensation.

In the past nearly all reports of anomalous pulmonary venous return have dealt with autopsy material. However, in 1947, Brantigan [3] discussed the surgical significance of anomalies of the pulmonary veins. He listed 14 more cases, reported by seven authors, which have appeared in the literature since Brody's review in 1942. For the thoracic surgeon, it is frightening to contemplate the possibility of removing one lung only to find that the circulation of the other lung drains into the major venous system. Hence, the significance of recognizing these anomalies at surgery. A diagnosis of complete drainage of pulmonary venous blood into the right auricle or its tributaries is of course difficult to establish fully without actual anatomical dissection, but with the aid of angiocardiography and cardiovascular catheterization Snellen and Albers [4] were able clinically to recognize four cases as probably belonging to this group. Survival in such instances depends on the presence of a cardiac septum defect. When the venous drainage from the lungs into the right auricle or its tributaries is incomplete, the commonest sites for drainage, in order of frequency, are the superior vena cava, the right atrium, and the left innominate vein. In those cases in which there is complete drainage of the pulmonary blood into the right auricle or its tributaries, the sites of anomalous

From the Pathology Department of the Glendale Sanitarium and Hospital.

1. Hughes, C. W., and Rumore, P. C.: Arch. Path. **37**:364, 1944.
2. Brody, H.: Arch. Path. **33**:221, 1942.
3. Brantigan, O. C.: Surg., Gynec. & Obst. **84**:653, 1947.
4. Snellen, H. A., and Albers, F. H.: Circulation **6**:801, 1952.

entrance of the pulmonary veins, in order of frequency, are the superior vena cava and its tributaries, the coronary sinus, the right atrium itself, the portal vein, and the inferior vena cava.

The available literature on the subject appears to include only three cases in which all the pulmonary venous return emptied into the ductus venosus. The first is reported by Ghon,[5] the second by Mehn and Hirsch,[6] and the third, reported recently, by Edwards and DuShane.[7] The case described here makes the fourth such listed. All have been of newborn children with similar clinical histories.

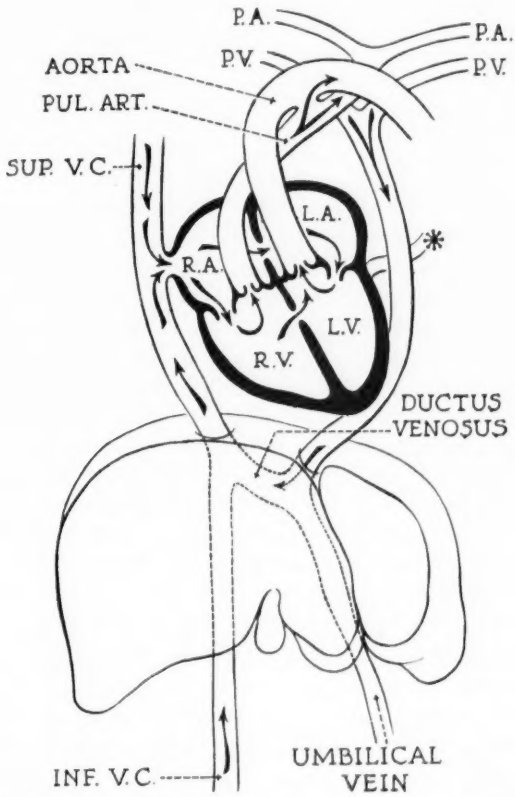


Diagram of circulation, front view. The asterisk denotes the persistent left superior vena cava entering the oblique vein of Marshall.

REPORT OF A CASE

A white girl weighing 2 lb. 14½ oz. (1,120 gm.) was born at the Glendale Sanitarium and Hospital March 25, 1952, on the service of Dr. Joseph Morreale. She was kept in an incubator and fed by gavage. Beginning March 30, she was frequently given oxygen because of cyanosis, which occurred especially after feedings. Adminstration of crystalline penicillin procaine G

5. Ghon, A.: Beitr. path. Anat. **62**:175, 1916.
6. Mehn, W. H., and Hirsch, F. E.: Am. J. Path. **23**:125, 1947.
7. Edwards, J. E., and DuShane, J. W.: Arch. Path. **49**:517, 1950.

(Crysticillin), 20,000 units daily, was begun April 2, 1952, because of low-grade fever. On April 4, oxytetracycline (Terramycin) therapy was started. On April 7, and following days her color became more dusky. Respirations became more labored and rapid, and the patient died April 11, 1952. She had gained 6 oz. (160 gm.) during this period.

A postmortem examination was made (only pertinent findings will be mentioned).

Respiratory System.—The trachea and bronchi contained a thick, purulent discharge. The lungs floated in water and grossly appeared to show areas of consolidation. Polymorphonuclear cells were seen in the alveoli on microscopic examination.

Cardiovascular System (Figure).—The heart was enlarged, especially the right auricle and ventricle. The foramen ovale was patent. A defect measuring 5 by 7 mm. was present in the upper portion of the interventricular septum. The ductus arteriosus was patent. The pulmonary veins combined to form a common pulmonary vein, which passed through the diaphragm to empty into the ductus venosus within the liver and thence into the inferior vena cava. Another anomalous mediastinal vein, not connected with the pulmonary system, emptied into the coronary sinus and no doubt represented a persistent left superior vena cava communicating with the coronary sinus through a persistent oblique vein of Marshall.

COMMENT

A persistent left superior vena cava is one of the commonest venous anomalies, and it can readily be explained by reviewing the embryology. Beattie,[8] in 1931, reported 3 cases and stated that 175 cases had appeared in the literature up to that time. In 1941 McManus[9] reported another case and stated that Papez[10] had compiled over 200 cases up to 1938. McManus also reviewed the embryology. In the early embryo a paired venous system is present. Thus two precardinal and two postcardinal veins, one on either side, unite to form the ducts of Cuvier, which empty into the sinus venosus. Later an anastomosis is established between the precardinal veins; gradually the part of the left precardinal vein proximal to the anastomosis atrophies and the anastomosis becomes the innominate vein. Occasionally the left precardinal vein persists as a left superior vena cava. When this occurs, the left duct of Cuvier persists as the oblique vein of Marshall and empties into the right auricle by way of the coronary sinus. Occasionally the oblique vein of Marshall is absent, and the persistent left superior vena cava ends in a closed sinus, as in a case reported by Prows[11] in 1943 as the eleventh such case.

Occasionally, startling anomalous connections between the pulmonary veins and the major venous system are encountered which are much more difficult embryologically to explain. These connections are explicable only on the basis of early embryonic capillary connections between the primitive vascular system and the lung bud. If the early pulmonary vein fails in its development to reach the left auricle, then some other anomalous pathway must be found. It is thought that the venous plexus covering the lung bud is derived from the splanchnic venous plexus. During development, the enlargement of certain channels in the primordial vascular system could readily account for these various anomalous connections.

Consideration of the circulation in the present case indicates that aerated blood from the lungs could reach the systemic distribution only by way of the patent

8. Beattie, J.: Canad. M. A. J. **25**:281, 1931.
9. McManus, J. F. A.: Canad. M. A. J. **45**:261, 1941.
10. Papez, J. W.: Anat. Rec. **70**:191, 1935.
11. Prows, M. S.: Anat. Rec. **87**:99, 1943.

foramen ovale and the patent interventricular septum after traversing a circuitous route through the diaphragm, liver, and right heart. As the blood was thereby forced to mingle with the systemic venous return, the child was constantly cyanotic.

The cyanosis was always worse after feeding, suggesting that either the common pulmonary trunk was somehow compressed at its diaphragmatic passage, owing to gastrointestinal filling, or that increased portal flow may have impeded the intruding pulmonary current as both competed for space in the hepatic venous drainage.

The finding of exacerbated cyanosis after feeding, in newborn infants in whom congenital malformations are suspected or are shown to exist, might warrant an exploratory operation for the purpose of diagnosis and possible surgical correction.

Correspondence

HOME PROGRAM MONOGRAPHS OF NATIONAL MULTIPLE SCLEROSIS SOCIETY

To the Editor:—I should like to thank you for the generous review of our Home Program monographs, additional copies of which are being sent to you with this letter.

My only revision is that inadvertently two minor errors have crept into your review which, I am sure, you will be anxious to correct so that our services may be more readily understood.

In the first place, there is no charge for these monographs when they are used for purposes pertaining to our program. Your reviewer, who stated "It would be wise if the National Multiple Sclerosis Society made these pamphlets readily available for doctors," apparently did not read the introductory remarks which clearly state that this material is sent without charge to physicians upon request.

If I can be of further service to you please do not hesitate to communicate with me.

HAROLD R. WAINERDI, M.D.,
Medical Director,
National Multiple Sclerosis Society, New York 17.

News and Comment

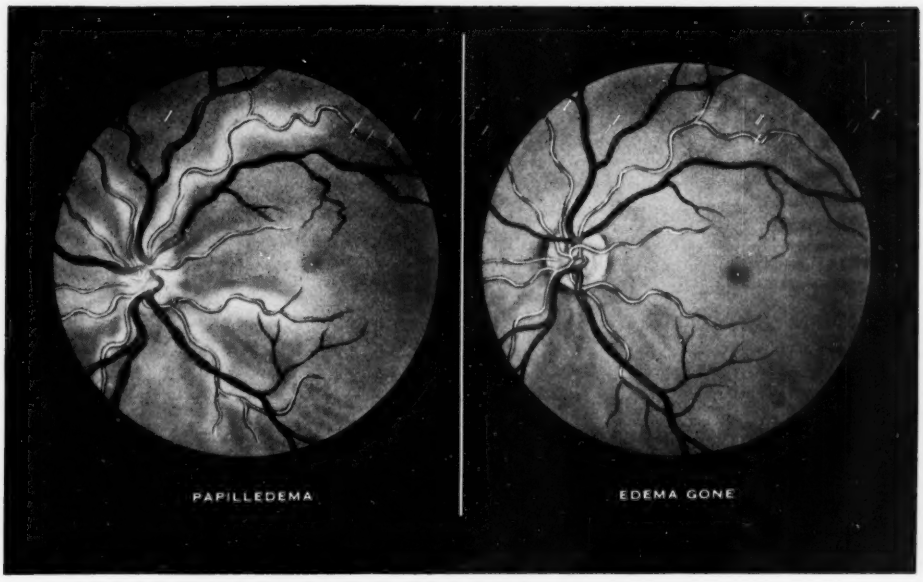
ANNOUNCEMENTS

Establishment of "Transplantation Bulletin."—To meet the need for continuous exchange of information on an informal basis among investigators in the clinic and the laboratory interested in problems of tissue transplantation it is proposed to issue a quarterly *Transplantation Bulletin*. The managing editors will be Herbert Conway, M.D., Cornell University Medical College, New York; Ernest J. Eichwald, M.D., University of Utah College of Medicine, Salt Lake City, and Nathan Kaliss, Ph.D., Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Blair O. Rogers, M.D., College of Physicians and Surgeons, New York, will be the associate editor.

This bulletin will maintain, and publish at least once yearly, a Transplantation Registry which will list all practicing physicians and research workers, both in the United States and abroad, interested in transplantation problems. The registry will cover the fields of plastic surgery, endocrinology, cancer, genetics, immunology, experimental morphology, etc. A bibliography will be maintained in these fields. The *Bulletin* will provide a medium for a rapid and informal exchange of information on problems and progress in the clinics and laboratories both here and abroad. It is emphasized that the *Bulletin* will not publish formal papers. However, brief comments on unreported data will be welcomed. It will, through a staff of corresponding editors, attempt to keep all members of the "Transplantation Registry" informed of forthcoming meetings of the professional societies at which there will be presentations dealing with aspects of transplantation. It will also try, through its corresponding editors, to have the subjects covered in a coordinated fashion at the meetings.

All workers in the fields of medicine and biology interested in tissue transplantation are asked to submit their name and field of interest to E. J. Eichwald, M.D., University of Utah College of Medicine, Salt Lake City. A subscription fee of $3, to cover the expenses of printing the *Bulletin* and maintenance of the Registry and bibliography, will be payable after the first issue of the *Bulletin* has appeared. The first issue is expected to appear in August, 1953.

Chicago Society of Internal Medicine.—At the Annual Meeting of the Chicago Society of Internal Medicine held May 25, 1953, Richard B. Capps was elected President; Arthur R. Colwell, Vice-President; Edwin N. Irons, Secretary-Treasurer, and Howard L. Alt, Frank B. Kelly, and Lowell R. Coggeshall to the Executive Committee.



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1. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., and Sieber, H. A.: J.A.M.A. *149*:215 (May 17) 1952.
2. Paton, W. D. M., and Zaimis, E. J.: Pharm. Reviews *4*:219 (Sept.) 1952.

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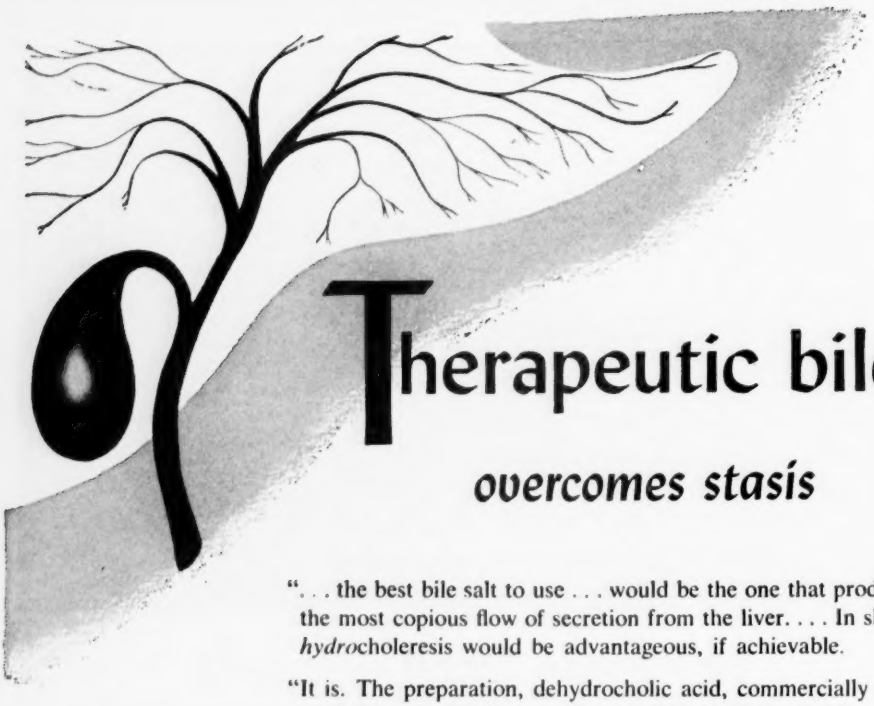

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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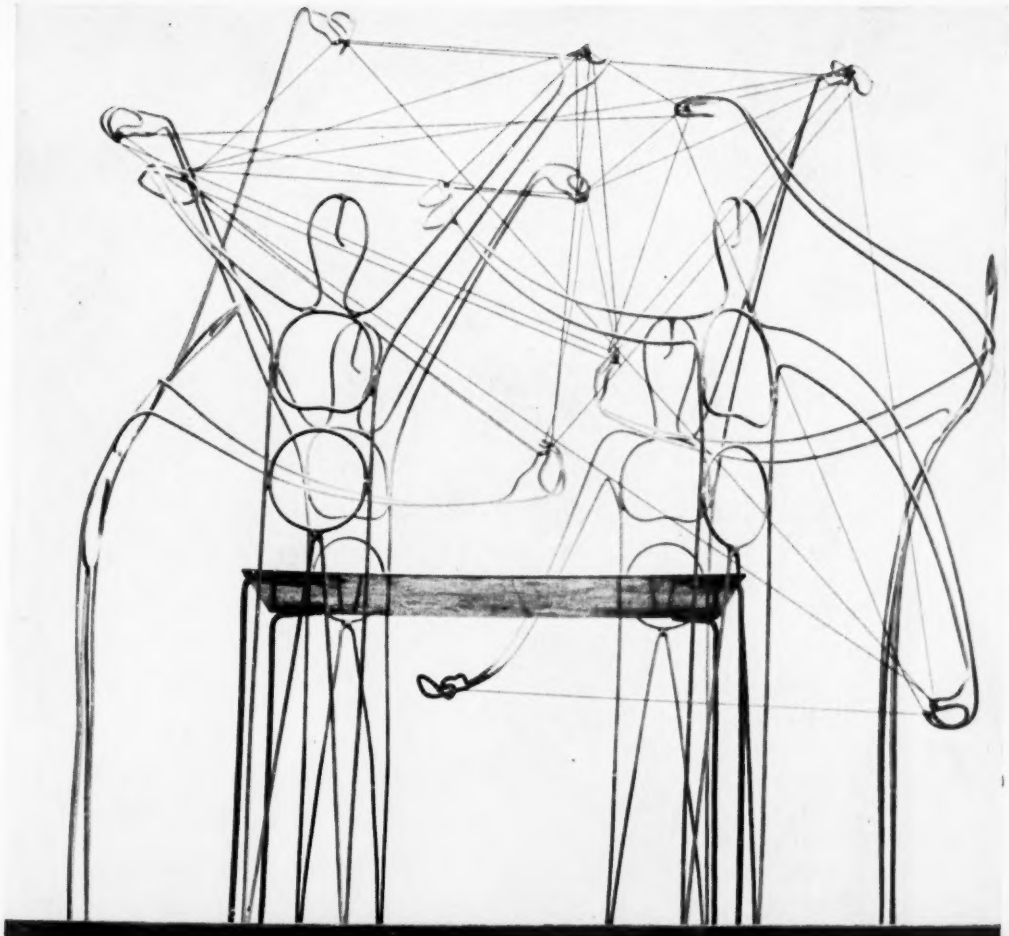

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1. Merryman, M. P.: The Use of the Low Sodium Diet. *South Dakota Jour. Med., & Pharm.*, 2:57, Feb., 1949.
2. Heller, E. M.: The Treatment of Essential Hypertension. *Canad. Med. Assn. Jour.*, 61:293, Sept., 1949.

*Author unidentified. From Mencken, H. L.: A New Dictionary of Quotations. New York, Alfred A. Knopf, 1942, p. 1057.

Neocurtasal, trademark reg. U. S. & Canada.